EXHIBIT 1

CONNETICS CORPORATION

Moderator: Pat O'Brien
April 26, 2005
3:30 pm CT

Operator: Good afternoon. My name is (Paige) and I will be your conference facilitator. At this time I would like to welcome everyone to the Connetics First Quarter Earnings conference call. All lines have been placed on mute to prevent any background noise.

After the speakers' remarks there will be a question and answer period. If you would like to ask a question during this time, simply press star then the number 1 on your telephone keypad. If you would like to withdraw your question, press star then the number 2 on your telephone keypad. Thank you.

I will now turn the call over to Pat O'Brien, Director of Investor Relations. Please go ahead, sir.

Pat O'Brien: Thank you and good afternoon, everyone. With me for today's conference call is Tom Wiggans, Chief Executive Officer, Greg Vontz, President and Chief Operating Officer, John Higgins, Chief Financial Officer.

I will begin the call by addressing our forward-looking statements. Following this, I will turn the call over to Tom Wiggans.

As a reminder, the statements made in this call represent our judgment as of April 26, 2005.

Our remarks and responses to questions during this conference call may constitute forward-looking statements, including plans, expectations and projections, all of which involve certain assumptions, risks and uncertainties that are beyond our control. And could cause our actual results to differ materially from these statements.

Those risks and uncertainties include among others, that sales growth and future product revenues may be lower or expenses may be higher than our projections in any quarter.

And that our clinical and regulatory expectations for our product candidates, including approval timeframes we expect, may not be met. And that the company may not be able to sustain profitability.

We encourage you to take the time to review our recent filings with the Securities and Exchange Commission and the first quarter earnings release issued earlier today, which present these matters in more detail.

Connetics does not undertake any obligation to update any forward-looking statements made during this call.

At this point, I'd like to turn the call over to Tom Wiggans.

Tom Wiggans: Thanks, Pat. And thanks, everybody for joining us today. I will give a general state of the business before I turn it over to John and Greg. And give

you an overview of another successful quarter, good corporate performance and continued momentum across the - all aspects of our business.

In the first quarter, we had a solid quarter for our core brands -- OLUX, Luxiq, Soriatane and Evoclin. Greg will be going into prescription trends for those. But it was a good quarter for us.

We continue to have good gains, good progress in our managed care area and our prescription growth. Also the Evoclin launch continues to go very well. We updated people on that at the analyst day and we'll give you some more information. But that is a very good launch for us.

Also in the first quarter - it's a very busy quarter for us in terms of our meetings and our attendance at many dermatology meetings, most notably the American Academy of Dermatology Meeting this year.

Once again I believe Connetics had a terrific visibility, terrific performance at the AAD, a great branding opportunity, good customer service opportunities and again, leading the way with many presentations and publications on our current and future products at that meeting.

In the first quarter we also moved to a new facility. Some of you have been out here to visit us. And I hope others can come to visit us in the facility.

Not only did we get a terrific real estate deal on the new facility, but importantly the company is back together now under one roof, resulting in I believe, a number of operational efficiencies, benefits, communication and continued excitement and momentum here at the company. So I hope as many of you as possible can come visit us.

We completed $200 million financing. Has nothing to do with moving into a new building. Did have a lot to do with the terrific financing environment, as well as Connetics being able to put more money in our war chest.

We have no identified uses for this money at the current time. However, as our size and our scope continues to expand, we feel it's important to have a war chest to take advantage of opportunities should they arise in the future.

We signed a commercial partnership with Ventiv, under which a new 50-person sales force will promote our products outside of the dermatology market. That is the successor to the UCB deal.

The UCB deal was a good one for us. But it was a corporate goal for us as many of you know, when UCB bought Celltech and terminated the relationship - for us to find an effective way to leverage our brands into non-dermatology markets. And we believe the Ventiv partnership is a great way to do that.

We had our analyst day on April 14. We were able to provide a terrific overview on our commercial opportunities and our pipeline.

And hopefully we were able to make the point that we believe we have the strongest pipeline in the dermatology sector -- not only a number of new clinical products that Greg will be updating you on, formulating candidates, but also our delivery platforms, not just our initial VersaFoam product but now our VersaFoam-Emollient Foam in our new products.

And those are being extremely well received in the clinical setting. And we believe will be extremely well received in the marketplace.

Regarding Velac, we are - we continue to be in active discussions with FDA on their review of our NDA. As we've moved through the review process, we've been pleased with the review.

And up to this point we've been in active communication with the agency. And have continued to be in active communication with the agency over the last several weeks, answering their questions as they finalize their review of the various sections.

As part of this review, we've recently received communications that indicated FDA were interpreting results of one of our preclinical studies in a different fashion than we did in our submission.

I realize over the past several weeks there's been speculation regarding the approvability of a new retinoid or approvability of a combo product. The question that they have asked is unrelated to either one of these subjects.

We conducted one of our preclinical studies in a transgenic mouse model. And in that study there was a positive response to our product. At the time, we carefully analyzed the results with a panel of leading experts in this model and leading toxicologists.

The outcome of that was that the experts advised us that this mouse model is known to have limitations. And they concluded that the positive response was a result of one of these limitations of the model.

Their advice is supported in fact, by other products which have had a positive finding in this model, resulting in a clinical hold only to be released later based upon submission of additional data.

And in fact, benzoyl peroxide, a commonly used OTC acne product and an ingredient in several prescription acne products, has Rx labeling that notes a positive result in this model.

Because up to this point FDA had not raised this issue with us, we were surprised to receive this information. However, we are in discussions with them on their question. And we expect to submit additional information well before the PDUFA date which further supports our original conclusion included in the NDA.

I would point out that as a rule, we do not feel it is appropriate frankly, to provide regular updates on our discussions with FDA.

And we do not intend to provide further updates on this until we have more definitive information because obviously this is limited information for you as well as for us. However, we felt it was important to take the opportunity to give you an update on this recent information.

While I realize that this question might raise more questions rather than answers for you just as it did us, I can tell you that we are very committed to working with FDA to get them the information so this issue can be resolved and enable us to launch Velac on schedule.

So with that overview, I'm going to turn it over to John to review the financials.

John Higgins: Tom, thank you. I'm going to review the first quarter results first and then walk through guidance for second quarter and full year.

First quarter results - we're pleased with our financial performance. Total revenues came in at 42.4 million. When we look at the breakout by product, Luxiq produced 5.7 million in revenue, OLUX - 15.8 million, Soriatane - 17.6 million and Evoclin - our first full quarter of sales - 3.1 million.

Greg will get into the prescription trend. We're very pleased with the prescription performance of these products and the revenue performance.

We are seeing with the maturity of our business, the revenues are impacted only slightly by our recently entered distribution service agreement, increased managed care contracting, as well as the mix of product size by product line.

That is, we have multiple sizes and the mix of sales between, for instance 50 and 100 grams continually changes.

In terms of royalty and contract revenue, we saw approximately $180,000 this quarter -- in line with our expectations.

Gross margins came in just over 91% -- slightly higher than forecast, principally due to the mix of Soriatane sales - the mix between U.S. and international. We do pay a royalty to Roche on international Soriatane sales.

Expenses came in slightly lower than expected for both SG&A and R&D. SG&A came in at 27.6 million and R&D at 5.8 million.

Net income for the quarter - we're pleased. We generated just over 1 million in net income, which produced earnings per share of 3 cents.

And with the net proceeds from our financing, we finished the quarter with cash - restricted cash of approximately $238 million.

Now I'd like to move to guidance. We've given of course, guidance on the full year as it relates to our recently announced partnership with Ventiv. Let me give some details on the second quarter and some further comments on our full-year guidance.

For the second quarter, we're forecasting revenues of $45 million to $47 million combined for total revenues on expenses of $34 million to $36 million.

The expense forecast is expected to be higher than the first quarter. And higher than we originally expected at the start of this year due - principally due to the Ventiv copromotion agreement, which was not expected at the start of this year.

We will incur launch and copromotion costs related to the Ventiv partnership. Of course, we will continue to spend heavily on what we believe is still the launch period of Evoclin. And of course we're budgeting for the Velac prelaunch activities -- a very important program for us.

In addition, we do expect the R&D costs to be higher as well in the second quarter over the first quarter due to the increased clinical activity. We're still developing Desilux in phase III studies. And now have two phase III trials ongoing for Primolux as well.

With this revenue and expense guidance, we forecast earnings per share on a fully diluted basis to be in the range of 6 cents to 8 cents for the second quarter.

When we look at the full-year guidance, we did raise revenue and expense guidance when we announced the Ventiv copromotion deal a couple of weeks ago.

The revenue guidance for 2005 is 195 million to 206 million -- increased originally from 190 million to 200 million.

On the expense side, we're forecasting expense in the range of 121 million to 128 million -- again an increase from our original guidance in light of the Ventiv copromotion expense structure. The original guidance was $116 million to $123 million.

We forecast the Ventiv deal would generate additional revenues for us but will be earnings neutral in 2005, yet earnings positive in 2006. Therefore our earnings per share guidance is unchanged for '05 at 88 cents to 92 cents.

Just a little more color on the business as now we move into the second quarter and have better visibility on the second half of 2005. We're very pleased with the way the business is advancing.

On the revenue side we do forecast in the second half of '05, growth of all of our existing four brands, notably with increased revenue really kicking in in the third and fourth quarter given our partnership with Ventiv promoting to the non-dermatology audience.

We are of course, forecasting the launch of Velac in the third quarter at this time with this guidance.

And I do want to comment that we've enjoyed strong fourth quarter revenues the last several years. It seems to be a very significant quarter for dermatology products and certainly we have included that in our assumptions.

On the expense side, we do forecast second half expenses will be lower than the first half. A couple of significant factors - the first half costs.

As we've discussed in the past, there are multiple major medical meetings we sponsor, sales and home office training that are first half of the year events. In addition, we are incurring significant launch activities for both Evoclin and Velac in the first half.

We do incur a higher administrative cost in the first half. And also, we believe at this time that the copromotion expenses for the non-derm channel may be higher as well in the first half.

So again, we do forecast lower SG&A in the second half. Also the R&D cost we expect to be lower as well as the clinical trial work will begin to wrap up.

On the amortization side, specific to our recent debt deal, we expect amortization to up slightly on an annual basis as we amortize our debt transactions over a ten-year life.

With just under $7 million in total expenses, the annual amortization cost for the next ten years will be about $670,000. That is an increase.

Just a final comment. Of course, this 2005 guidance assumes that Velac launches in the third quarter. If there is a delay in that timeline there will be an impact on our financial forecast and we will update guidance accordingly.

Greg, I'll turn it over.

Greg Vontz: John, thanks. Let me start my comments off with some highlights from our first quarter.

As you know, first quarter is typically a very challenging quarter for us just in terms of all the activities, meetings that go on and time with dermatologists at their office. And this quarter was no exception to that.

In spite of those environmental circumstances, we had a strong showing in the first quarter.

If we look at the Rx performance in Q1 of 2005 versus the same period in 2004 for Luxiq, we have a 12% increase in prescriptions, achieving $66,000 and change in Q1 '05 for Luxiq.

Also a 12% growth in Rxs for OLUX, moving up to almost 112,000 prescriptions for the first quarter of 2005.

And excitingly for Soriatane, in a same period comparison, a 4% growth rate for Soriatane, achieving close to 31,000 prescriptions in the first quarter of 2005.

And undoubtedly the real bright spot in this quarter was the enthusiastic reception by physicians and patients to Evoclin, which closed out the first quarter with 29,000 prescriptions. So a very strong showing by Evoclin.

A couple of other points of note for the quarter. While we always struggle a little bit in January and February again because of the meetings, March comes back strong. This was the case again for our Rx trends.

In March, OLUX reached an all-time high for the 100 gram trade size, exceeding 34,000 prescriptions in the month. And Luxiq was just shy of an all-time high for itself.

In keeping with the trend of all-time highs, in March we also achieved for the first time a new record high for Soriatane since it has been introduced into the market, with specific momentum in the 10 gram size, which we believe is indicative of growing interest in low-dose utilization as well as in combination with biologics.

While it's difficult to equate the increase in Soriatane in the first quarter with the potential change in the prescribing environment for the biologics, we did notice a decline in Enbrel in the treatment of psoriasis in January and February.

So all in all, given the time out on the market for our customers and the many meetings and activities, we had a strong first quarter, especially buttressed by the fact that the markets - the overall steroid markets were down for mid and high-potency products about 3%.

As we look forward to the second quarter, historically it is a strong quarter for us and we certainly look to continue that momentum and historical trend. Additionally, our expanded sales force is really starting to hit their stride now. And we look for exciting activities from them in the second quarter.

And as Tom mentioned and was - as introduced in our analyst day recently, our Ventiv promotional activities to more than 8000 physicians outside of dermatology now is well underway.

We are having encouraging reports from our managers that are spending time in the field with these new customers and our new representatives. So all in all, a lot of momentum going into the second quarter.

Now let me shift my comments from our commercial activities to progress on the product development front.

Our clinical operations team and our product development organization continue to drive very aggressively in pushing our development programs ahead. And this quarter was no different.

We were pleased to announce at our analyst day the unblinding of our phase II results for Desilux. I'll remind you that Desilux is our low-potency topical steroid in our emollient foam vehicle.

The results that we saw in that trial were certainly encouraging, showing a 53% response rate of clear or almost clear for Desilux, a 12% response rate for the placebo emollient foam. But again, we're always tempered in our enthusiasm for these data as these are merely a small, phase II sizing study.

Additionally, many thanks to our clinical operations team for their incredible work. I'm pleased to announce that they have now concluded enrollment in our Desilux phase III program, enrolling more than 550 patients in the complete phase III trial, which now puts us well on our way and on track to file an NDA for Desilux before year end.

In terms of our other phase III development program with Primolux, I'll remind you that is formerly our OLUX-EF program. We have made good progress on that program as well. We now are actively enrolling in two phase III programs -- one in atopic dermatitis, the other in psoriasis.

The early enrollment trends are positive. And I think as Tom mentioned, we continue to be encouraged by the reception of this vehicle by clinicians in the clinical research phase. Here again we believe we are on track with an ambitious timeline for an NDA filing at year's end.

And finally, with regards to an update on our clinical programs, calcipotriene in VersaFoam-EF is moving along well.

We have been in discussions with the agency and would appear to be on track for a Q3 '05 clinical start for this program. And we look forward to updating you on future calls as this exciting program gets underway.

So with that, that concludes my comments. Let me now turn it back over to Tom.

Tom Wiggans: Great, John. Thank you very much. We will now open it up for some questions. Operator?

Operator: At this time I would like to remind everyone, if you would like to ask a question, press star then the number 1 on your telephone keypad. We'll pause for just a moment to compile the Q&A roster.

We are still compiling the Q&A roster. Your first question comes from Elliot Wilbur with CIBC World Markets.

Elliot Wilbur: Good afternoon, guys. And thanks for taking the question. I understand the commentary about the slowing rate of growth in the steroid market in the first quarter.

And, you know, obviously it's somewhat seasonal due to all the meetings and the like. But this is the first time we've actually seen Luxiq, OLUX sales down sequentially.

And I guess, you know, outside of the market conditions, what's also changed is that you have a lot more sales force muscle behind the product. So it would just seem that that should have offset, you know, the slight deterioration in growth.

And I'm wondering if there's anything else there that could have impacted reported sales such as returns or a new distribution services agreement with another wholesaler? Or something that might have caused you to, you know, pare down ex-factory sales?

Man: Elliot, thanks. As Greg pointed out, first quarter over fourth quarter they were down.

We certainly don't want to use it as an excuse but we can't overemphasize that the first quarter is generally - it's not a tough quarter for us. It's a fun quarter because there are a lot of meetings.

And we're out there, we're kicking off the year. But we're spending a lot of money because we're in meetings. And physicians aren't writing a lot of prescriptions because they're in meetings.

If you look at year-over-year, we actually were pretty happy with the growth in Luxiq and OLUX. I agree with you, it is challenging to continue to grow these products five and six years old.

However, we expect them to grow from our own expanded sales force. And we expect Ventiv to have an impact. When we look at the UCB data, they did have an impact with these products in non-derm markets.

So that's a bit of a long answer to your question, Elliot. But I think we are okay with the first quarter over fourth quarter decline this year, we're happy with the year-over-year growth and we look forward to growing the products the rest of the year.

Elliot Wilbur: Okay. Then I had one follow-up question for John on the SG&A line. Looking at your guidance for the second quarter - and I guess I'm going to make the assumption that we'll probably see SG&A go up modestly at least.

Then if I think about your full-year guidance, it kind of puts you at a low 20-something run rate. And I guess that's sort of below the rate that you were at in the fourth quarter of '04, which didn't reflect the full sales force cost yet.

So, you know, I understand that you've got a lot more visibility on some of the discretionary spend items than we do. But I'm just trying to get a little bit more comfortable that we can kind of get back down to that low 20s rate.

John Higgins: Yes, Elliot. Good question. And your analysis generally is accurate. First and second quarter SG&A are going to be the high quarters for the year. Q3 and Q4 will come down. We haven't given specific items but the general level that you're describing makes sense.

I think what's significant is that we did have a sales force expansion. It was - actually I think they were recruited in September and on the street the first week of October. So that was a full quarter impact.

Not only have we invested significantly in Evoclin launch activities but also to really arm, so to speak, the expanded sales force with the training and the samples that they need, we have invested significantly in all of our brands from a promotional perspective.

That coupled with higher copromotion expenses, as well as the unanticipated Ventiv costs in the second quarter were really the driving factors why first half SG&A will certainly be higher than the second half SG&A.

Elliot Wilbur: All right. Thank you. Those are my only questions.

Operator: Your next question comes from Deb Knobelman with Piper Jaffray.

Deb Knobelman: Hey guys. A couple of questions. My first question, as much as you can answer this, on Velac - just give us a little more feel on how long it will take to do the additional trials on Velac.

And if the FDA does decide to push out your PDUFA date, when you might expect to hear back from them on that.

Man: Well Deb, let me ask - answer that two ways. First, (we did) - this information is recent. We're giving it to you in pretty real time so we don't have a lot of color on it.

However, it is our plan to submit additional information to them well before the PDUFA date. So if I suggested at this time there was additional trials to do, that's not the case.

So we will be submitting additional information to them. And we expect to do that in the next several weeks.

Deb Knobelman: Okay. So you don't need to do any additional even preclinical trials?

Man: We do not have 100% clarity on if there's any additional things we have to do. What we do know at this time and in response to their question, we have the information and we're preparing to submit that.

Deb Knobelman: Okay. Great. And then just - second part, kind of following up on what Elliot was asking, I guess if you do assume that Velac launches in the third quarter, you still would anticipate that Q3 would be down sequentially from Q2 in terms of SG&A spend?

Man: Yes.

Deb Knobelman: Okay. Is that because the bulk of sort of the sampling and everything else comes in the second quarter?

Man: No. Sampling of course, will kick up at the time of launch. And - but there's - part of it is across all four of our product lines, investment across all the sampling activity. I think proportionately the sampling costs will be lower in the third quarter.

But also significantly, before the launch of Velac and any revenue of course from that brand, we're investing now and preparing for that. So we're incurring expenses across all these existing brands plus for the brands that are not launched.

Deb Knobelman: Right. Okay. And then just one more question on R&D spend. I have here in my notes that you guys have guided to 28 million to 30 million in R&D spend for '05 in total.

Is it going to be lower than that now or is that - what is the current run rate on that, I guess?

Man: That - we have not given express guidance since the beginning of the year. The run rate will likely come in slightly below that original guidance.

Deb Knobelman: Okay. Okay great. Thanks, guys.

Man: Thank you.

Operator: Your next question comes from David Buck with Buckingham Research Group.

David Buck: Yes. Thanks for taking the question. The first one's for Tom on Velac. You mentioned the preclinical positive finding in the rat study.

Can you just give a little bit more clarity on what that was? And, you know, give us - just in follow up, give us some comfort that this is the type of situation that wouldn't require another preclinical trial at least.

And then I have a follow up.

Tom Wiggans: David, first of all that was a mouse, not a rat. But it's probably a technicality.

You know, I'm just not - I'm not prepared to go into a lot of depth right now. We just got this information. I think we understand the information that we're looking for and we're going to be submitting some additional information.

And right now beyond that, I don't think we're prepared to comment. We - I realize the information may be incomplete but we've told you pretty much what we know.

David Buck: Okay. And one John on just the SG&A side. Can you give us a little bit more color on just the size of the SG&A spending for the Ventiv Health agreement?

The guidance for this quarter obviously is, you know, is a lot lower than the current consensus. So just give us some sense of where the Ventiv spending comes in. Thanks.

John Higgins: Yeah. Sure. Absolutely. The increase in expense guidance for the year in '05 -- of course it's a partial year -- is 5 million for Ventiv. And we increased the revenue range from 5 million to 6 million.

So you can assume that all of that is relating to Ventiv with some of the expenses being frontloaded in the second quarter as we train, deploy the field force and supply them with samples. So that is clearly a big driver.

Consistent with our original plan and we discussed this on our first - fourth quarter call in January, the first half of the year, again significant expenditures, not only in product sampling but also the launch activities around Evoclin and Velac.

Also I'll comment that the first quarter expenses for SG&A, in fact came in slightly lower than our forecast. And largely due to timing of various factors throughout the first and second quarter.

David Buck: Okay. And if I could sneak in one more, just on the inventories that you have in the trade, did you experience any trade inventory (destocking)? I know that

you've talked about fee-for-service agreements. And particularly on the steroid franchise it looks like obviously you trailed script growth.

But, you know, can you give us some sense of what happened on the trade inventory side?

John Higgins: Sure. Essentially no change in inventory levels. And regarding perhaps the value for Rx, I think what is significant just to play off of Tom's comment earlier, the reality of maturing brands and now OLUX and Luxiq are in their fifth and sixth - entering their seventh year.

The reality is not only are the DSAs, the Distribution Service Agreements, new in terms of a cost of our distribution process, but also as we have more mature brands, there is a bigger bite for the managed care contracting. There's a bigger bit, so to speak, out of revenues for Rx for Medicaid.

And also, I believe another analyst inquired about return. It's not really significant to note separately but obviously with more mature brands, returns are going up as we would forecast. That increases the reserve against those sales modestly.

So it's very much in line with our forecast and expectations, consistent with maturing product line and the reality of these several components.

David Buck: Okay. Thank you.

Operator: Your next question comes from Angela Larson with C.E. Unterberg and Towbin.

Angela Larson: Thank you for taking the question. I want to go back to the SG&A spend. I think what we're struggling with is does this imply that you're training your sales force for the Velac launch before you got actual approval?

Man: Angela, no. I don't think you can make that interpretation from the SG&A spend. But certainly a portion of the SG&A spend in Q2 relates to supporting Evoclin and the rapidly growing base of business for that product, as well as preparing for Velac introduction.

Man: Yeah. I think the hesitation, Angela - we were all kind of looking ourselves, shaking our head. So that's not the case.

But clearly there are prelaunch activities. But as far as bringing everybody in for a launch meeting, that's not scheduled yet.

Angela Larson: So when we try to, you know, put our arms around what is different in third quarter versus second and first quarter, it's prelaunch activities but not the actual sales force training.

Man: The actual - Angela, a lot of - as you might imagine, there's a lot of prep work that goes into a launch meeting. That's why those expenses were recognized in advance. The actual training itself is a fairly modest expense in the whole process.

Angela Larson: Okay.

Man: That's right. Yeah. And also the Ventiv - of course in the first half of the year, the UCB contract costs were fairly high. Ventiv, of course, it's a brand new relationship.

The startup costs will be frontloaded to a certain extent. And that revenue, we won't begin to realize really until they're out in the market meaningfully for several months. So I think that's significant.

Essentially right now, Evoclin and our past products, OLUX notably and Luxiq - we really started to invest in the launch of those brands post launch. With Velac we are preparing the market for launch and incurring Velac's launch costs as well.

So all of that is hitting. It's just a variety of factors that are hitting, to a certain extent frontloaded in the first half of 2005.

Man: Yeah. And...

Man: Those are the variable expenses.

Man: Yeah. And Angela, I will add again, for those of you who were at the analyst day, I think you saw the UCB Rx impact, which was dramatic in terms of the impact they had with our brands outside of derm, as was their lack of impact once the merger was announced.

We recognize that the Ventiv startup has costs associated with it in the second quarter. And frankly, we thought it was an investment worth making.

And we're excited about their contributions for the rest of the year, knowing that the second quarter is - we're taking a little bit of a hair cut on EPS on the second quarter as a result of that.

Angela Larson: Okay. And one quick question on the Velac outcome. The positive result in the transgenic mouse -- what kind of clinical risk does that raise? Right now we're kind of left with no information.

Man: Well obviously we have looked at this carefully as we submitted the NDA and had a lot of expert opinions. I mean our view is it has absolutely no relevance to clinical.

But it doesn't mean that we don't have some additional information that we can supply the FDA on additional preclinical work that we've done. And data that we have.

Man: Angela, let me also add a couple of quick comments. With regard to clinical outcomes, we saw nothing whatsoever in our clinical trials.

Additionally, I will make mention that there are currently products in the market that have a benzoyl peroxide component that in their labeling they mention a TgAC study positive finding. But yet they are approved products on the market.

Angela Larson: Okay. Thank you.

Operator: Your next question comes from Mark Taylor with Roth Capital Partners.

Mark Taylor: Good afternoon. Thanks for taking the question. Just two real quick. On the Soriatane revenue achieved in the first quarter, could you break down the international?

And then secondly on Velac, regarding CMC's side of the equation, have - has that pretty much been taken care of to your satisfaction so far? Perhaps maybe a plant inspection by FDA upcoming?

Man: Mark, I'll answer the Soriatane question. We do not break out in detail international and U.S.

Specifically for Soriatane, I will say at the time that we announced that business being added to our Soriatane line, that it was approximately 1 million a month. And that's the general trend we've seen the last several months.

Mark Taylor: Okay.

Man: Mark, with regards to your question on the CMC front with Velac, we've been in a very positive and active dialog with the agency on the CMC front. And have a sense that they are soon to conclude that part of the review.

And would not be surprised at some point in the future for them to have a visit.

Mark Taylor: Thank you very much.

Operator: Ladies and gentlemen, we have reached the end of the allotted time for questions and answers. Mr. O'Brien, are there any closing remarks?

Tom Wiggans: I think Mr. O'Brien will turn it over to me. Once again, thanks to everybody. Had a good turnout today. Appreciate the questions.

It was a good first quarter and we look forward to keeping you informed of our progress through the rest of the year. Thank you very much.

Operator: This concludes today's Connetics First Quarter Earnings conference call. You may now disconnect.

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EXHIBIT 2

Environmental Health PERSPECTIVES
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Transgenic Mouse Models: Their Role in Carcinogen Identification

John B. Pritchard, John E. French, Barbara J. Davis, and Joseph K. Haseman

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Transgenic Mouse Models: Their Role in Carcinogen Identification

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Running Head: Transgenic Models

Abbreviations (Text):

NTP	=	National Toxicology Program
MAPKK	=	mitogen-activated protein kinase kinase
Trp53+/-	=	Trp53 heterozygous null allele (+/-) mouse
Tg.AC	=	Tg.AC (*v-Ha-ras)* mouse
*ras*H2	=	hemizygous for the human *c-Ha-ras* transgene
ILSI	=	International Life Sciences Institute
ROC	=	Report on Carcinogens
IARC	=	International Agency for Research on Cancer

Abbreviations (Tables):

+	=	positive
-	=	negative
±	=	equivocal
f	=	feed
g	=	gavage
d	=	dermal
ip	=	intraperitoneal injection
i	=	inhalation
sc	=	subcutaneous
wb	=	whole body routes of exposure
nt	=	not tested or no published record
sal	=	*salmonella* mutagenicity assay
mn	=	*in vivo* micronuclei genotoxicity assay

Keywords:

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Abstract:

This report examines existing data on the use of transgenic mouse models for identification of human carcinogens. It focuses on the three most extensively studied of these mice – Trp53+/-, Tg.AC, and RasH2 – and compares their performance with the traditional 2-year rodent bioassay. Data on a total of 99 chemicals were evaluated. Using the IARC/ROC calls for the carcinogenicity of these chemicals to humans as the standard for comparison, a variety of potential testing strategies were evaluated ranging from individual transgenic models to combinations of these 3 models with each other and with traditional rodent assays. The individual transgenic models made the "correct" calls (positive for carcinogens; negative for noncarcinogens) for 77-81% of the chemicals, with an increase to as much as 88 % using combined strategies (e.g., Trp53+/- for genotoxic chemicals and RasH2 for all chemicals). For comparison, identical analysis of chemicals in this data set that were tested in the 2-year, 2-species rodent bioassay yielded "correct" calls for 69 % of the chemicals. Although the transgenic models had a high percentage of correct calls, they did miss a number of known or probable human carcinogens; whereas, the bioassay missed none of these chemicals. Therefore, "mixed" strategies using transgenic models and the rat bioassay were also evaluated. These strategies yielded ~85 % correct calls, missed no carcinogens, and cut the number of positive calls for human non-carcinogens in half. Overall, the transgenic models performed well, but important issues of validation and standardization need further attention to permit their regulatory acceptance and use in human risk assessment.

Introduction:

The National Toxicology Program (NTP) is charged with the responsibility for evaluating the toxicity and carcinogenicity of environmental agents, developing and validating improved testing methods, and strengthening the science base in toxicology. A variety of endpoints are used to assess the systemic toxicity of environmental chemicals, but the mainstay of the chemical carcinogenesis effort has been the 2-year rodent bioassay. This highly standardized method has been widely adopted throughout the world. However, like any other approach it has its strengths and weaknesses. In particular, the 2-year assay is expensive, both in resources and time required and in the numbers of animals needed. Thus, the advent of transgenic and gene knockout technology in the early 1980's and increasing knowledge of the mechanisms involved in carcinogenesis, led a number of investigators to examine whether faster, less costly, and more predictive models might be developed. NIEHS has been actively involved in this effort for more than a decade and several model systems utilizing transgenic and knockout models have been investigated (Bucher 1998;Eastin, et al. 1998;Tennant 1993;Tennant, et al. 1995).

Transgenic models have a number of potential advantages for use in carcinogen identification programs. For example, because tumors arise more quickly in the genetically engineered models, the assays can be more rapid. For the studies reviewed here, the assay length was 24-26 weeks, significantly shorter than the standard 2-year rodent bioassay. Transgenic models may also provide the opportunity to reduce animal numbers used in testing. Shorter assays using fewer animals could also reduce the overall cost of testing programs. However, proprietary issues and the limited availability of some models may impact cost savings. Furthermore, with appropriate model selection, it may become possible to more accurately predict the human response, contributing directly to the ease and effectiveness of risk assessment and regulatory decisions.

Finally, by virtue of the specific genetic modification(s) in transgenic models, it should be possible to gain additional insights into the mechanisms involved in tumor induction and development. Such insights would facilitate identification of important mechanisms participating in the tumor response and chemical features associated with carcinogenesis.

Although they have great promise, transgenic models also have actual or potential limitations for use in a carcinogen identification effort. For example, many current transgenic models (including those evaluated here) have mutations in only one pathway that may, or may not, be relevant to human cancer processes for a given chemical. In addition, the specific gene defect may influence tumor development and type, increasing the difficulty of modeling the human response. Likewise, the strain (genetic) background can influence tumor type, incidence, and location. Thus, short-term, gene-specific transgenic assays may lose biological information obtained in longer-term bioassays, *e.g.,* multiple target organ effects and/or interactions of time and age that are important in chemical carcinogenicity. These issues do not preclude the use of transgenic models, but they must certainly be considered in their development and selection, and in interpretation of data obtained using transgenic models.

Given the potential and the limitations of the transgenic models, the goals of the current assessment are to (1) review progress in this field of research, (2) determine if the models reviewed show sufficient merit for use in a carcinogen identification program, and (3) identify research needs and knowledge gaps that should be addressed to increase the effectiveness of transgenic models.

Review of Research Progress:

Many transgenic models are available for various investigational uses. However, three transgenic models have been most widely used for carcinogen identification: Trp53+/-, Tg.AC, and RasH2. These three models were selected for this assessment because they have the extensive data set needed for this analysis. Their selection does not indicate that they are deemed superior *a priori* to other transgenic models.

Extensive recent reviews of these three models have been published (17-24) and only their main features are briefly reviewed here. They were developed based on dysregulation of either the Trp53 tumor suppressor gene or the *ras*-protooncogene, both of which are critical to cancer development and represent the two main classes of human cancer genes. The p53 protein suppresses cancer in humans and rodents and is mutated or dysfunctional in more than 50 % of all cancers (Donehower, et al. 1992;Hollstein, et al. 1991;Weinberg 1991a). As a transcription factor, p53 regulates the activity of a variety of genes involved in cell cycle arrest, apoptosis, anti-angiogenesis, differentiation, DNA repair, and genomic stability (el-Deiry 1998;Prives and Hall 1999). The *ras* protooncogene protein (H-, K, and N-*ras* isoforms) is integral to cell proliferation through signaling by growth factors and noxious agents (chemicals, UV radiation, etc.) that act via the mitogen-activated protein kinase kinase (MAPKK) pathway (Campbell, et al. 1998;Gupta, et al. 2000;Pruitt and Der 2001). Activation and dysregulation of *ras* through mutations at specific sites within the gene are often observed in both human and rodent cancers (Bos 1989;Hruban, et al. 1993;Vogelstein, et al. 1990;Yunis, et al. 1989). In addition, increased expression of oncogenic *ras* protein is often seen during tumorigenesis by aneuploidy of the *ras* bearing chromosomes, which may be analogous to over-expression of induced transgenic *ras* protein. Overall, *ras* is over-expressed in well over 50 % of all cancers.

The *Trp*53 heterozygous null allele (+/-) mouse: This model uses B6129 N5 mice heterozygous for a wild type Trp53 tumor suppressor gene and a null allele that is not transcribed or translated (Donehower, et al. 1992;Harvey, et al. 1993). These Trp53 heterozygotes (+/-) have a low spontaneous tumor incidence up to 9 months of age, but have increased spontaneous tumor rates thereafter with approximately 50 % survival at 18 months. Exposure to positive control and test agents between 7 and 33 weeks of age is relatively free of the development of spontaneous tumors, thus allowing a clear distinction between induced and sporadically occuring tumors that may confound long term chronic cancer bioassays (Haseman and Elwell 1996;Karstadt and Haseman 1997). It appears to be particularly useful as an *in vivo* test for mutagenic carcinogens (Donehower, et al. 1992;Eastin, et al. 1998;Harvey, et al. 1993;Kemp, et al. 1993;Kemp, et al. 1994;Tennant, et al. 1995). In human cancers, where mutations have been found in up to 50 % of all tumors (Greenblatt, et al. 1994;Hollstein, et al. 1991), point mutations or deletions in one allele of the Trp53 gene that create a heterozygous allelic state are usually accompanied by loss of the normal allele (loss of heterozygosity or LOH) (Weinberg 1991b). Since Trp53 +/- mice only carry one copy (germ line) of the gene, these mice were expected, according to the Knudson *et al.* two-hit hypothesis (Knudson 1996;Knudson, et al. 1975), to show a shorter latency period for tumors induced by genotoxic agents. However, there is evidence that the acceleration of tumorigenesis in Trp53 +/- mice may be due to a gene dosage effect and a haploinsufficient phenotype such that a second (p53 LOH) event is not required (French, et al. 2001;Venkatachalam, et al. 1998).

The Tg.AC (*v-Ha-ras*) mouse: The Tg.AC transgenic mouse model provides a reporter phenotype (skin papillomas) in response to either genotoxic or non-genotoxic carcinogens, including tumor promoters (Spalding, et al. 1999;Spalding, et al. 1993;Tennant, et al. 1999).

Tg.AC mice are hemizygous for a mutant *v-Ha-ras* transgene. The model was developed by Leder et al. (Leder, et al. 1990), with an inducible □-globin promoter driving the expression of a mutated *v-Ha-ras* oncogene and is regarded as a genetically initiated model. With the exception of the bone marrow, constitutive expression of the transgene cannot be detected in adult tissues. The transgene is transcriptionally silent until activated by full-thickness wounding, UV irradiation, or specific chemical exposure (Cannon, et al. 1997;Trempus, et al. 1998). Topical application of carcinogens to the shaved dorsal surface of Tg.AC mice induces epidermal squamous cell papillomas or carcinomas, a reporter phenotype that defines the activity of the chemical. The oral route of administration can also generate tumor responses in the skin of Tg.AC mice and in addition lead to squamous cell papillomas and/or carcinomas of the forestomach. To date, the appearance of either spontaneous or induced tumors has been shown to require activation of transgene expression. However, the mechanism of response by the Tg.AC model to chemical carcinogens is not yet understood.

The *ras*H2 mouse: The rasH2 mouse is hemizygous for the human *c-Ha-ras* transgene under control of its endogenous promoter and enhancer sequences. It was developed by Saitoh *et al.* (Saitoh, et al. 1990) in CB6F1 mice to evaluate the association of chemically induced transgene expression and tumor induction (Katsuki, et al. 1991;Yamamoto, et al. 1996;Yamamoto, et al. 1998a). The transgene encodes a prototype c-H-ras gene product, p21 that does not induce transformation in NIH3T3 cells. Approximately 3 copies of the human transgene were integrated into the mouse genome in a tandem array through pronuclear injection (Suemizu, et al. 2002). Expression of the transgenic protein is observed in normal tissues and increased approximately 2-fold in chemically induced tumors (Maruyama, et al. 2001). Mutation of the endogenous mouse ras genes or of the transgene is infrequent and unpredictable (Katsuki, et al.

1991); suggesting that a 2-3-fold increase in *ras* protein expression is sufficient to cooperate with other carcinogen-induced changes (genetic and/or epigenetic) to predispose this mouse to development of neoplasia.

Merits of the Models:

Data Collection – To assess the potential merit of the three transgenic models in a research and testing program, we assembled available information on responses to chemical treatment in each model (Tables 1-3). The primary sources of these data were the recent publications of the International Life Sciences Institute (ILSI) Assay Working Groups for the Trp53+/-, Tg.AC, and RasH2 Mouse Alternative Models (Popp 2001;Robinson and MacDonald 2001), NTP evaluations, and published independent laboratory research using alternative or conventional rodent models for carcinogen identification (For specific references see Tables 1-3). The resulting data set consists of 99 chemicals that were tested at the maximum tolerated dose (MTD) or proportional fractions of MTD as determined by toxicokinetic and range finding studies in the test strain using positive and negative controls groups and non-genetically altered coisogenic reference controls. In reviewing this literature, it was apparent that dosing routes, study duration, number of animals per group, and extent of histopathologic evaluation varied between studies and chemicals. Despite these limitations, for the purposes of this analysis, peer-reviewed published findings were accepted as reported.

Criteria for Analysis – Because the goal of the NTP carcinogenicity testing is prediction of human carcinogenicity of chemicals, the merit of the transgenic models was evaluated by determining their ability to identify human carcinogens. Classification of human carcinogens was based on evaluations by the NTP Report on Carcinogens (ROC) and the International Agency for

Research on Cancer (IARC) chemical evaluations/classifications. Both the NTP and IARC assessments are based on comprehensive evaluations of all relevant human and animal data from the published literature. The designation of an agent as a "known human carcinogen" by the IARC (Group 1) or the NTP ROC requires definitive data from human epidemiological studies, or strong mechanistic data from human systems in conjunction with similar mechanistic and cancer data from experimental animals. Less convincing evidence (*e.g.,* limited human data and/or sufficient animal data) will generally lead to the designation of the agent as a "probable (Group 2A) or "possible" (Group 2B) human carcinogen by IARC or a "reasonably anticipated" human carcinogen NTP ROC. A chemical that shows inadequate evidence of carcinogenicity in humans and animals will generally result in an IARC designation of "not classifiable" (Group 3). The NTP ROC has no equivalent and does not list such chemicals. Rodent carcinogenicity was not used as the primary targeted response in our analysis. Nevertheless, for completeness we did consider the correlation of each transgenic model with the outcomes of NCI/NTP long-term rodent tests. We also examined whether these transgenic assays were more, or less, accurate in predicting human carcinogenicity of genotoxic versus non-genotoxic chemicals, as defined by either a positive result in the Salmonella (Ames) test and/or in vivo rodent micronucleus assay.

A total of ninety-nine chemicals have been studied in one or more of these three transgenic models. For this analysis, these chemicals were divided into three groupings: **(i)** Known human carcinogens (IARC Group 1 and/or NTP ROC "known" – 14 chemicals, Table 1); **(ii)** Probable/ Possible human carcinogens (IARC Groups 2A and 2B or NTP ROC "reasonably anticipated" –32 chemicals, Table 2); and **(iii)** Chemicals with inadequate evidence of carcinogenicity (IARC Group 3, NTP bioassay negative, and/or not listed by ROC or IARC – 53 chemicals, Table 3).

Tables 1-3 identify each chemical by CAS number and give the IARC and/or the NTP ROC evaluations. For those chemicals evaluated in the NTP rodent bioassay, carcinogenicity results are given for each sex-species group (male rats, female rats, male mice, female mice). Genotoxicity outcomes from the Salmonella (Ames) assay and the *in vivo* micronuclei assays are also given. Finally, the results of carcinogenicity testing in each of the three transgenic models are given. The route of administration is noted, as well as the published reference source. For chemicals tested more than once in the transgenic models, each result is given separately.

For each of the transgenic models and for the rodent bioassay, a chemical is designated as a carcinogen if positive (carcinogenic) effects were found in one or more of the sex-species groups. Similarly, a chemical found to be positive in either the Salmonella assay or the *in vivo* micronuclei assay is considered to be genotoxic.

Analysis of the Models -- Based on the 99 chemical database from Tables 1-3, ten possible strategies were considered for using transgenic models to identify chemicals as known or suspected human carcinogens or as noncarcinogens. For comparison, the standard two-year, two-species rodent bioassay and a modified strategy using the rat bioassay in conjunction with genotoxicity were also analyzed in an identical fashion. Thus, twelve strategies in all were considered. They are:

Strategy 1: Trp53+/- model

Strategy 2: Trp53+/- model, but only for genotoxic chemicals

Strategy 3: Tg.AC model

Strategy 4: RasH2 model

Strategy 5: Trp53+/- model for genotoxic chemicals; RasH2 model for nongenotoxic chemicals

Strategy 6: Trp53+/- model for genotoxic chemicals; RasH2 model for all chemicals

Strategy 7: Trp53+/- model for genotoxic chemicals; Tg.AC model for nongenotoxic chemicals

Strategy 8: Trp53+/- model for genotoxic chemicals; Tg.AC model for all chemicals

Strategy 9: NTP Bioassay

Strategy10: NTP Rat Bioassay plus the Tg.AC model for nongenotoxic chemicals or the Trp53+/- model for genotoxic chemicals

Strategy 11: NTP Rat Bioassay plus the RasH2 model for nongenotoxic chemicals or the Trp53+/- model for genotoxic chemicals

Strategy 12: NTP Rat Bioassay plus genotoxicity

When evaluating strategies that were conditional on genotoxicity (Strategies 5-8, 10-11), the following conventions were established: (i) a chemical was considered genotoxic if either the Salmonella or in vivo micronuclei assays were positive; (ii) a chemical was considered non-genotoxic only if both assays were negative; and (iii) when a chemical's genotoxicity could not be determined definitively (*i.e.,* negative in one assay and not tested in the other), the chemical was excluded from the analysis, unless the genotoxicity status of the chemical had no impact on the transgenic mouse result (*i.e.,* both transgenic models were positive or both were negative).

A valid transgenic rodent model should successfully identify (test positive) the IARC/NTP known or suspected human carcinogens listed in Tables 1 and 2. Likewise, such a model should identify as noncarcinogens (test negative) those chemicals in Table 3 that were shown in NTP long-term bioassays to be negative. While many of the remaining chemicals in Table 3 were positive in a long term rodent bioassay, these results were not considered by the IARC and/or NTP ROC to be sufficiently convincing to merit the categorization of the chemical as a known, possible, probable, or reasonably-anticipated human carcinogen. For these chemicals, it is

uncertain if the response of the transgenic models should be positive or negative as carcinogens. Thus, our initial analysis (Table 4) included only those Group 3 chemicals with negative results in the NTP rodent bioassay. Table 5 examines the same data set as Table 4, but considers each IARC/ROC classification separately to insure that pooling carcinogen groups in these analyses did not lose important distinctions between assay responses to strong or weak carcinogens.

In addition, as summarized in Table 6, we have conducted a second analysis in which all chemicals in Table 3 are regarded as human noncarcinogens, *i.e.,* we have assumed, for the sake of direct comparison between transgenic and traditional NTP bioassays, that more extensive testing of these chemicals would confirm their lack of human carcinogenicity. This assumption permits exactly the same criteria to be applied to all strategies, transgenic and traditional alike. Finally, although human carcinogenicity was used as the targeted response in our analysis, a similar analysis was conducted in which the transgenic assay responses were compared with the results of the NTP bioassay (Table 7).

Results and Discussion:

Scope of analysis — Before discussing the analysis itself, it is critical to reiterate the precise limitations and assumptions implicit in our analysis. First, this evaluation was limited to those chemicals with definitive published transgenic results available at the time of our analysis. We recognize that this is a dynamic field of research. Thus, additional transgenic studies will become available over time, and it is possible that some chemicals listed in Tables 1-3 could be reclassified after consideration of such new data. However, we suggest that the analyses for these 99 chemicals are sufficiently robust that the addition, subtraction, and/or re-assignment of chemicals will not alter the conclusions, provided that uniform criteria are applied.

Second, optimal protocol designs for specific transgenic animal cancer bioassays have not been identified and validated. Thus, the study designs that form the basis of this evaluation may differ from each other with regard to study duration, sample sizes, dose selection strategy, number of doses, tissues examined, methods of statistical analysis, historical controls, and the use of positive and negative controls.

Third, we made no interpretative decisions ourselves in regard to study results. For assessments of possible human cancer risk, we relied upon the authoritative judgments of the IARC and the NTP Report on Carcinogens. Likewise, we accepted the study authors' interpretations of the data. However, there was uniformity of study design and interpretation for a sizable number of the studies involved in the ILSI Alternatives to Carcinogenicity consortium. It was beyond the scope of this research analysis to reevaluate and reinterpret each individual study.

Fourth, we recognize and acknowledge that a "positive" transgenic study may reflect a wide range of carcinogenic responses, with some positive results being limited to a marginal increase in a single tumor type in a single sex-species group, while others reflect striking multi-site, multi-sex, carcinogenic effects. While future refinements in statistical evaluation may permit sub-classification and rank order documentation for the various "positive" transgenic responses, we have not attempted to do so at this stage in the development of transgenic rodent bioassays.

Finally, we recognize that certain chemicals listed in Table 3 may ultimately be shown to be "known" or "suspected" human carcinogens, especially those with positive rodent bioassay results. However, our current state of knowledge does not permit a higher classification of these chemicals. As noted below, the frequency of positive transgenic results for Table 3 chemicals was essentially the same for those chemicals that were evaluated by the IARC (and assigned to Category 3) and those that were not yet evaluated and are thus unclassified. This suggests that there are few, if any, important human carcinogens among the "unclassified" chemicals in Table 3.

Performance of strategies _ The overall performance of each transgenic strategy is summarized in Table 4. With the caveat that data on all chemicals were not available for each model and thus, that the subset of chemicals actually tested in each model may influence the specific outcomes reported, each of the three transgenic mouse models predicted human carcinogenesis for 77-81 % of the chemicals studied in that model, ranging from 77 % for the Trp53+/-, 78 % for the Tg.AC, and 81 % for the RasH2. Use of the Trp53+/- for only genotoxic chemicals increased its predictiveness to 84 %. The combined strategies that use more than one transgenic model (Strategies 5-8; as defined above) were somewhat more predictive, ranging from 78-88 %.

The best strategy (Trp53+/- for genotoxic chemicals and RasH2 for all chemicals; Strategy 6) correctly predicted the human outcome for 88 % of the agents (Table 4). Strategy 8 (Trp53+/- for genotoxic chemicals and Tg.AC for all chemicals) was only slightly less predictive (85 %).

Our initial analysis (Table 4) defined the targeted population of "human carcinogens" as the pool of chemicals from Tables 1 and 2, in which IARC classifications ranged from 1 to 2B. A further breakdown of these chemicals is given in Table 5. Note that **(i)** the transgenic models (considered collectively) are more apt to be positive for the more certain human carcinogens (IARC Categories 1 and 2A) than for the less certain human carcinogens (Category 2B); **(ii)** there is a striking difference in the proportion of positive transgenic responses between the 1/2A/2B chemicals and the Category 3 chemicals or those not evaluated; and **(iii)** the IARC Category 3 chemicals and those not evaluated show a similar rate of overall transgenic responses – indicating that most of the unclassified chemicals listed in Table 3 may be human noncarcinogens.

Our initial analysis (Table 4) was somewhat restrictive, in that it defined human noncarcinogens as being only those chemicals from Table 3 with negative NCI/NTP rodent bioassay results. However, Table 5 suggests that it is reasonable to expand this classification and regard all Table 3 chemicals as human noncarcinogens. This analysis is summarized in Table 6, which allows more direct comparison of the performance of the transgenic models with the traditional NTP two-species bioassay, transgenic and traditional testing strategies each show strengths and weakness. Importantly, these strengths and weaknesses differ. For the transgenic models, particularly the RasH2 and the Trp53+/-, there are relatively few positive findings for noncarcinogens (*i.e.,* Group 3 chemicals, either known negatives or chemicals unlisted by

IARC/ROC, that gave evidence of carcinogenicity in the assay). In fact, as shown in Table 4, RasH2 and Trp53+/- have no positive results for noncarcinogens if those Group 3 chemicals that lack a negative rat and mouse bioassay are eliminated from the analysis (in effect, eliminating those chemicals with greater uncertainty as to their carcinogenic potential). The Tg.AC model was more prone to this type of error than the other two transgenic models reviewed (Tables 4 and 6). The combined transgenic strategies (Strategies 5-8) did not improve predictability.

A more frequent shortcoming of the transgenic models (including, those strategies using multiple transgenic models) was the number of negative tests for known or suspected human carcinogens, *i.e.,* those listed in Tables 1 and 2 (Tables 4 and 6). For example, even the most predictive combination (the combined results of Trp53+/- for genotoxic chemicals plus Tg.AC for nongenotoxic chemicals; Strategy 7) still had 6 negative results for IARC/NTP known carcinogens among the total of 49 chemicals tested in both (Table 6).

In contrast, the NTP two-species bioassay identified all IARC/NTP known/probable human carcinogens (Tables 1 and 2). Thus, as shown in Table 6 (Strategy 9), among the 58 chemicals evaluated in the NTP bioassay, there were no negative results for known human carcinogens. However, this is not without a downside in the form of numerous positive findings for chemicals that are considered to be noncarcinogens in humans (Table 3). In this data set, there were 18 positive assay results for IARC/ROC noncarcinogens among a total of 58 chemicals tested, or 31 % (Table 6). Certainly, there is a cost of this type of error as well, specifically unneeded regulation and/or additional testing. It is this propensity for positive findings for chemicals considered to be human noncarcinogens that yielded the surprisingly low 69 % concordance between the standard NTP bioassay and human cancer – surprising because many of the ROC

and IARC calls are based in large part on animal data and the NTP bioassay in particular. In fact, all three transgenic models had a modestly higher concordance with human carcinogens (Tables 1 and 2) than the rodent 2-year bioassay (Trp53+/- 81 %, RasH2 75 %, and Tg.AC 74 %; Table 6). Of course, this difference is also reflected in the modest success (54-78 %) of the transgenic models as predictors of the bioassay response (Table 7).

It should be emphasized that it is possible that many of the 18 NTP rodent carcinogens labeled in our analysis as "Positive for Noncarcinogens" (Table 6, Strategy 9) may ultimately prove to be actual human carcinogens, as additional data becomes available. However, at this time the positive rodent data are not sufficiently compelling for the IARC or the NTP ROC to consider these chemicals to be known, probable, possible, or reasonably anticipated human carcinogens. In those rare cases where the IARC and ROC disagreed (*e.g.,* DEHP) we used the most recent call. Moreover, these 18 chemicals collectively were positive in only 27 % (8/30) of the three transgenic assays evaluated, as compared with 66 % (29/44) positive transgenic assays conducted on the 24 known/probable carcinogens. This difference strongly suggests that the transgenic assays are selectively identifying the trans-species carcinogens.

Since both transgenic models and the bioassay have strengths and weakness in correctly identifying carcinogenic chemicals, we examined the performance of composite strategies using both transgenic and conventional rodent models to determine if such a strategy might capitalize on the strengths of both types of models. Strategies 10 and 11 address this possibility (Table 6). Strategy 10 (rat bioassay for all chemicals plus the Trp53+/- model for genotoxic agents or the Tg.AC for non-genotoxic chemicals) provided an improvement in performance. Overall concordance increased to 84 % versus the 69 % of the bioassay itself. More importantly,

negative results for known carcinogens were completely eliminated and positive findings for noncarcinogens were reduced to 16 % (9/57) versus the 31 % (18/58) for the bioassay. A similar strategy (Strategy 11) substituting RasH2 for Tg.AC gave very similar results, with an overall concordance of 85 % (44/52), or just 15 % (8/52) with positive results for noncarcinogens.

For those chemicals evaluated in both the NTP bioassay and the transgenic models, the substitution of the transgenic models (Strategy 10: Trp53+/- for genotoxic chemicals; the Tg.AC for non-genotoxic chemicals) for the B6C3F1 mouse used in the standard bioassay resulted in a net reduction of four positive findings. Four chemicals (coconut oil diethanolamine, diethanolamine, N-methyloacrylamide and methylphenidate) were negative in the transgenic models and the NTP rat bioassay. In the B6C3F1 mouse, the first two of these chemicals produced liver tumors (both sexes) and kidney adenoma (males only). N-methyloacrylamide produced tumors of the Harderian gland, liver, lung, and ovary. Methylphenidate produced liver tumors only. None of these chemicals has been classified as a known/probable human carcinogen by the IARC or the NTP ROC (Tables 1-3).

Historically, genotoxicity has proven to be an important clue as to the likely carcinogenesis of chemicals (Ashby and Tennant 1991;Shelby 1988). In addition, as shown in Table 4, it increases the predictiveness of Trp53+/- model. Thus, to provide a more complete assessment of possible testing strategies, we compared an additional strategy (#12, Table 6) that consists of substitution of genotoxicity data for the transgenic models to be used in concert with the rat bioassay (Strategies 10 and 11, Table 6). Strategy 12 does, like the bioassay itself, avoid negative results for known carcinogens. It also has modest concordance with human carcinogenesis 67 % (44 of

66), but it has 22 positive results for noncarcinogens out of 66 chemicals (33 %). A number of the other strategies do better.

Conclusions _ Given the complementary strengths demonstrated by the transgenic models and the 2-year rodent bioassay as presented above and summarized in Table 6, it appears that a strategy employing both types of models would have advantages over either alone. Thus, Strategies 10 and 11 that employ the standard rat bioassay in conjunction with Trp53+/- for genotoxic chemicals and Tg.AC or RasH2 for non-genotoxic chemicals are promising, based on their performance with these 99 chemicals.

Research Needs:

This analysis demonstrates that transgenic models have the potential to play an important role in identification of potential human carcinogens. However, several research needs and data gaps remain to be addressed to insure that the use of transgenic models has been adequately evaluated and that protocols have been optimized or standardized for such use, critical requirements for the regulatory acceptance of transgenic model data and it's use in human risk assessment.

Validation of study design _ The study design for each transgenic model must be rigorously evaluated and optimized for the testing paradigm employed (*e.g.,* toxicity, mutagenicity, or carcinogenicity). Therefore, additional research will be required for each model evaluated and used in the NTP testing program. As mentioned previously, the testing strategies, animal numbers, duration of dosing, extent of pathology and interpretation of results varied among the studies evaluated. In particular, an optimal design for transgenic models has not yet been identified that clearly eliminates the potential for false negatives in carcinogen identification. Two possible strategies for increasing the power of the study (thereby reducing the negative results for known human carcinogens) are to increase the sample size beyond the 15 animals per group commonly used and/or to increase the duration of the study to allow more time for tumors to develop. The performance of the transgenics under these different conditions should be thoroughly investigated and standardized. A perhaps less obvious possibility would be to compile a rigorous historical control database for the various transgenic models and to make use of this information in "weight-of evidence" decisions. Many of the tissues in the transgenic mouse models have a low spontaneous tumor incidence. Thus, the occurrence of two or three of these tumors in a dosed group in a given study, although perhaps not statistically significant when tested against the concurrent controls, may nevertheless be significant when the low

historical control incidence is taken into account. For example, three of the seven negative results for known/suspected carcinogens associated with the RasH2 model (cyclosporin A, melphalan, and 1,4-dioxane) produced tumor effects that were considered equivocal. Had it been possible to consider these tumor responses in the context of a large historical control database, certain of these borderline cases might have been regarded as biologically significant, thereby reducing the number of incorrect findings.

Improve understanding of chemical outcomes _ One problem in our analysis was in identifying a rational basis to explain discordant results. For example, the most significant shortcoming of a combined (transgenic plus rat bioassay) strategy was not the negative results for known carcinogens, but rather the apparent number of positive chemicals in the rat bioassay that are not listed as known or reasonably anticipated to be human carcinogens (*e.g.,* the 10 of the 59 chemicals for Strategy 11; Table 6). How might this be improved? First, it might be possible to design additional studies to investigate whether or not these are truly noncarcinogenic chemicals. As discussed above, the targeted response in our investigation is imperfect, as it represents a scientific judgment by IARC and/or the NTP ROC regarding potential carcinogenicity based on available data. In many cases, the existing data are insufficient for a definitive decision to be made. Additional research could reduce the number of positive results for supposed noncarcinogens simply by revealing that certain of these chemicals are in fact carcinogens. Other options that might be considered to reduce this type of error include a rat transgenic model (if done in a manner that did not yield negative results for known carcinogens) or improvements in the design of the rat bioassay itself.

Development of chemical database to validate transgenics _ The data set summarized in Tables 1-3 may provide an important resource if appropriate statistical considerations could be developed to allow selection of an informative subset of chemicals for evaluation of new models and/or modification of current protocols. Such a set of chemicals that represents a spectrum of mechanisms or modes of action consistent with human carcinogenesis would not only be valuable in the context of the models discussed above, but would lend themselves to the evaluation and validation of any new model, transgenic or otherwise.

Development of Models The current analysis examined the Trp53+/-, Tg.AC, and RasH2 transgenic models because these models had the most complete data sets available. Other models are also under evaluation at the NIEHS/NTP (p16*Ink4a* and p19*Arf* deficient mice) or elsewhere (*XPA*-*Trp*53 deficient mice). A new generation of transgenic models is also currently being developed (Berns 2001), such as one incorporating a point mutation in k-*Ras* (Johnson, et al. 2001), or models subject to premature aging or having telomere dysfunction (Artandi and DePinho 2000;Rudolph, et al. 2001). If the NTP incorporates transgenic models into routine testing, it must necessarily include a strong research program aimed at developing the transgenic models appropriate for chemical carcinogenesis investigation and identification of carcinogens of the greatest presumptive risk to humans. As our analysis shows, the best strategy for testing may be combining different transgenic models depending on their particular attributes and utility. Thus, the NTP should actively develop such an arsenal of models. Likewise, site specific or mechanism-specific models could be developed and used with great impact in both basic research and carcinogen identification. The NTP could also develop or support research to evaluate transgenic rats or in assessment of possible refinements in the 2-year rat bioassay.

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Table 1. Comparison of results from 14 known human carcinogens[1] tested in rodent NCI/NTP cancer bioassays, Salmonella (Sal) and/or in vivo micronuclei (Mn) genotoxicity assays and/or 3 transgenic mouse cancer bioassays. Individual results were found in the cited references in parenthesis or at the IARC(IARC 2002) or the US NTP database(NTP 2002). NCI/NTP peer-reviewed conclusions are reported for male rat, female rat, male mouse; or female mouse, respectively. Results from transgenic models are presented as the summary conclusion for each route of exposure using one or both sexes of the strain used.

Agent	CAS No.	IARC	NTP ROC	NCI/NTP Bioassays	Genotoxicity (Sal; Mn)	p53+/-	Tg.AC	RasH2
Benzene	71-43-2	1	Known	+;+;+;+ g(NTP 1986d)	-;+	+ g; + g (French, et al. 2001;Storer, et al. 2001)	+ d; + g (Blanchard, et al. 1998;Spalding, et al. 1999)	+ g (Yamamoto, et al. 1998b)
Cyclophosphamide	6055-19-2	1	Known	+;+;+;+ip (Weisburger 1977)	+;+	+ g (Storer, et al. 2001)	±d; +g (Eastin, et al. 2001)	± g;+ g; + g (Usui, et al. 2001;Yamamoto, et al. 1998b)
Melphalan	148-82-3	1	Known	+;+;+;+ ip (Weisburger 1977)	+;+	+ ip;+ ip (Eastin, et al. 1998;Storer, et al. 2001)	±d; +g (Eastin, et al. 1998;Eastin, et al. 2001)	± ip(Yamamoto, et al. 1998b)
Cyclosporin A	79217-60-0	1	Known	nt	-;-	- g;+ f;+f (Eastin, et al. 1998;Storer, et al. 2001)	+d; ± f (Eastin, et al. 1998;Eastin, et al. 2001)	± g (Maronpot, et al. 2000;Usui, et al. 2001;Yamamoto, et al. 1998a)
Diethylstilbestrol	56-53-1	1	Known	nt	-;nt	- sc ;+ f (Eastin, et al. 1998;Storer, et al. 2001)	+d; -g (Eastin, et al. 1998;Eastin, et al. 2001)	+ f (Usui, et al. 2001)
Estradiol, 17-□	50-28-2	1	Reasonable	nt	-;-	± g; - g (Storer, et al. 2001)	+d; -g[2] (Eastin, et al. 2001)	- g (Usui, et al. 2001)
TCDD[3]	1746-01-6	1	Known	+;+;+;+ f (NCI/NTP 1982b)	-;nt	- g (Eastin, et al. 1998)	+ d (Eastin, et al. 1998)	nt
UVR (312-450 nM)	NA	1	Known	nt	+;+	+ d (Jiang, et al. 1999)	+ d (Trempus, et al. 1998)	nt
Asbestos fibers	1332-21-4	1	Known	-;-;nt;nt d (NTP 1988a)	nt;-	+ ip (Marsella, et al. 1997)	nt	nt

[1] As identified by the International Agency for Research on Cancer (IARC) and/or the NTP 9th Report on Carcinogens, revised January 2001.

2 Both dermal and gavage studies in the Tg.AC mice employed ethinyl estradiol (CAS No. 57-63-6), a synthetic form of estradiol, 17□.

3 2,3,7,8-Tetrachlorodibenzo-para-dioxin

Agent	CAS No.	IARC	NTP ROC	NCI/NTP Bioassays	Genotoxicity (Sal; Mn)	p53+/-	Tg.AC	RasH2
Beryllium	7440-41-7	1	Known	nt	-;-	+ i (Finch, et al. 1998)	nt	nt
Plutonium^{239}	NA	1	Known	nt	+;+	+ i (Finch, et al. 1998)	nt	nt
Cobalt^{60}(LET)	NA	1	Known	nt	-;+	+ wb (Kemp, et al. 1994)	nt	nt
Sodium arsenate	7784-46-5	1	Known	nt	nt;nt	nt	-d (Germolic, et al. 1997)	nt
Thiotepa	52-24-4	1	Known	+;+;+;+ g (NCI/NTP 1978f)	+;nt	nt	nt	+ ip (Yamamoto, et al. 1998b)

Table 2. Comparison of results from 32 suspected human carcinogens[1] tested in rodent NCI/NTP cancer bioassays, Salmonella and/or in vivo micronuclei genotoxicity assays and/or 3 transgenic mouse bioassays. Individual results are found in the cited references in parenthesis or in the IARC(IARC 2002) or in the US NTP database(NTP 2002). NCI/NTP Peer-reviewed conclusions are reported for male F344 rat, female F344 rat, male B6C3F1 mouse; or female B6C3F1 mouse, respectively. Results from transgenic models are presented as the summary conclusion for each route of exposure using one or both sexes.

Agent	CAS No.	IARC	NTP ROC	NCI/NTP Bioassays	Genotoxicity (Sal; Mn)	p53+/-	Tg.AC	RasH2
p-Cresidine	120-71-8	2B	Reasonable	+;+:+;+ f (NTP 1979)	+;-	+ f; + g (Storer, et al. 2001;Tennant, et al. 1995)	+ d (Tennant, et al. 1999)	+ f (Yamamoto, et al. 1998b)
Glycidol	556-52-5	2A	Reasonable	+;+;+;+ g (NTP 1990c)	+;+	- g (Tennant, et al. 1999)	- d; - g (Tennant, et al. 1999)	+ g (Usui, et al. 2001)
Phenolphthalein	77-09-8	2B	Reasonable	+;+;+;+ f (NTP 1995c)	-;+	+ f;+ f (Dunnick, et al. 1997)	nt	- f (Koujitani, et al. 2000)
4-Vinyl-1-cyclohexene diepoxide	106-87-6	2B	Reasonable	+;+;+;+ d (NTP 1989a)	+;+	+ d (Tennant, et al. 1995)	- d (Tennant, et al. 1999)	+ d (Yamamoto, et al. 1998b)
2,4-Diaminotolulene	95-80-7	2B	Reasonable	+;+;-;+ f (NCI/NTP 1979a)	+;-	± f (Eastin, et al. 1998)	+ d (Eastin, et al. 1998)	nt
Chloroprene	126-99-8	2B	Reasonable	+;+;+;+ I (NTP 1998b)	-;-	- i (French 2001)	- i (French 2001)	nt
Pentachlorophenol	87-86-5	2B	Not Listed	+[2];-;+;+ f (NTP 1999f)	-;-	- f (Spalding, et al. 2000)	+ d (Spalding, et al. 2000)	nt
Phenacetin	62-44-2	2A	Reasonable	nt	-;nt	- f; - g (Storer, et al. 2001)	-d; -f (Eastin, et al. 2001)	+ f (Yamamoto, et al. 1998b)
Phenobarbital	50-06-6	2B	Not Listed	nt	wk+;nt	- f;- f (Sagartz, et al. 1998;Storer, et al. 2001)	ia d; ia g; ia f (Eastin, et al. 2001)	-g (Usui, et al. 2001)
Chloroform	67-66-3	2B	Reasonable	+;-;+;+ w (Griesemer and Cueto 1980)	-;+	± g (Storer, et al. 2001)	- g (Delker, et al. 1999)	- g (Usui, et al. 2001)

[1] "Probable" (2A) or "possible" (2B) human or "reasonably anticipated" to be a human carcinogen as identified by the International Agency for Research on Cancer (IARC) and/or NTP Report on Carcinogens (9th NTP ROC, revised January 2001), respectively.

[2] Positive in 1000 ppm 1 year exposure stop study but not with 2 year exposure to technical grade pentachlorophenol (technical grade, TR349; purified, TR483)

Agent	CAS No.	IARC	NTP ROC	NCI/NTP Bioassays	Genotoxicity (Sal; Mn)	p53+/-	Tg.AC	RasH2
Benzo[a]pyrene	50-32-8	2A	Reasonable	nt	+;nt	+ d,g (Martin, et al. 2001)	+ d (Martin, et al. 2001)	nt
Dimethylnitrosamine	62-75-9	2A	Not Listed	nt	+;nt	+ w (Harvey, et al. 1993)	nt	nt
7,12-Dimethylbenzanthracene[3]	57-97-6	NE	Not Listed	nt;nt;+;+ d, i-p (NTP 1996)	+;+	+ d (Kemp, et al. 1993)	+ d (Spalding, et al. 1993)	nt
N-ethyl-N-nitrosourea	759-73-9	2A	Not Listed	nt	+;+	+ ip (Mitsumori, et al. 2000)	nt	+ ip (Yamamoto, et al. 1998b)
2-Amino-3-methylimidazo[4,5-f]quinoline	76180-96-6	2A	Not Listed	nt	+;+	+ g (Nagao 1999)	nt	nt
N-Butyl-N-(4-hydroxybutyl) nitrosamine (BBN)	64091-91-4	2B	Not Listed	nt	nt;-	+ w (Ozaki, et al. 1998)	nt	nt
N-methyl-N-nitrosourea	684-93-5	2A	Not Listed	nt	nt;+	+ip (Yamamoto, et al. 2000)	nt	+ ip (Yamamoto, et al. 1998b)
Urethane	51-79-6 5	2B	Reasonable	nt	+;+	+ ip (Carmichael, et al. 2000)	+d (Spalding, et al. 1993)	+ ip (Mori, et al. 2000;Umemura, et al. 1999)
Oxymetholone	434-07-1	2A	Reasonable	±;+;nt;nt (NTP 1999e)	-;-	- g (Stoll, et al. 1999)	+ d (Stoll, et al. 1999)	nt
1, 2-Dimethylhydrazine	540-73-8	2A	Not listed	nt	-[4];nt	nt	nt	+ d (Yamamoto, et al. 1998b)
1,4-Dioxane	123-91-1	2B	Reasonable	+;+;+;+ w (NCI/NTP 1978b)	-;+	nt	nt	± w (Yamamoto, et al. 1998b)
Ethylene thiourea	96-45-7	2B	Reasonable	+;+;+;+ f (NTP 1992a)	-;nt	nt	nt	+f (Yamamoto, et al. 1998b)
Methylazoxymethanol acetate	592-62-1	2B	Not listed	nt	-;nt	nt	nt	+ sc (Yamamoto, et al. 1998b)

[3] Reasonably anticipated to be a human carcinogen based on its use a prototypical mutagenic carcinogen used in initiation-promotion and complete carcinogenicity studies.
[4] 1,2-dimethylhydrazine dihydrochloride (CAS No. 306-37-6) tested in *Salmonella* mutagenicity assay.

Agent	CAS No.	IARC	NTP ROC	NCI/NTP Bioassays	Genotoxicity (Sal; Mn)	p53+/-	Tg.AC	RasH2
Procarbazine	366-70-1	2A	Reasonable	+;+;+;+ ip (NCI/NTP 1979d)	+;+	nt	nt	+ip (Yamamoto, et al. 1998b)
4,4'-Thiodianiline	139-65-1	2B	Not listed	+;+;+;+ f (NCI/NTP 1978c)	+;nt	nt	nt	+f (Yamamoto, et al. 1998b)
MNNG	70-25-7	2A	Reasonable	+;+;+ d ip (NTP 1996)	+;nt	nt	nt	+ g (Yamamoto, et al. 1998b)
Cupferron	135-20-6	2A	Reasonable	+;+;+;+ f (NCI/NTP 1978d)	+;nt	nt	nt	+ f (Yamamoto, et al. 1998b)
N-nitrosodiethylamine	55-18-5	2A	Reasonable	nt	+;nt	nt	nt	+ ip (Yamamoto, et al. 1998b)
Dimethylvinylchloride	513-37-1	2B	Not listed	+;+;+;+ g (NTP 1986b)	+;+	nt	+ d (Stoll, et al. 1999)	nt
4-Nitroquinoline N-oxide[5]	56-57-5	NE	Not listed	nt	+;nt	nt	nt	+sc (Yamamoto, et al. 1998b)
4-Hydroxyaminoquinoline-1-oxide[5]	4637-56-3	NE	Not listed	nt	+;nt	nt	nt	+ ip (Yamamoto, et al. 1998b)
Mirex	2385-85-5	2B	Reasonable	+;+;nt;nt f (NTP 1990d)	-;nt	nt	+d (Stoll, et al. 1999)	nt

[5] Reasonably anticipated to be a human carcinogen based upon its use as a prototypical mutagenic carcinogen for mechanistic investigation of chemical carcinogenesis.

Table 3. Comparison of results from 52 suspected human carcinogens[1] tested in rodent NCI/NTP cancer bioassays, Salmonella and/or in vivo micronuclei genotoxicity assays and/or 3 transgenic mouse bioassays. Individual results are found in the cited references in parenthesis or in the IARC(IARC 2002) or in the US NTP database(NTP 2002). NCI/NTP Peer-reviewed conclusions are reported for male F344 rat, female F344 rat, male B6C3F1 mouse; or female B6C3F1 mouse, respectively. Results from transgenic models are presented as the summary conclusion for each route of exposure using one or both sexes.; w, water (routes of exposure); nt, not tested or no published record.

Agent	CAS No.	IARC	NTP ROC	NCI/NTP Bioassays	Genotoxicity (Sal; Mn)	p53+/-	Tg.AC	RasH2
p-Anisidine	90-04-0	3	Not Listed	±;-;-;- f, (NCI/NTP 1978e)	+;-	- f (Tennant, et al. 1995)	- d (Tennant, et al. 1995)	- g (Maronpot, et al. 2000)
1-Chloro-2-propanol	127-00-4	NE	Not Listed	-;-;-;- w (NTP 1998a)	+;nt	- g (Tennant, et al. 1999)	- d (Tennant, et al. 1999)	nt
2,6-Diaminotoluene	820-40-5	NE	Not Listed	-;-;-;- f (Battershill and Fielder 1998)	+;-	- f (Eastin, et al. 1998)	- d(Eastin, et al. 1998)	nt
8-Hydroxyquinoline	148-24-3	3	Not Listed	-;-;-;- f (NTP 1985b)	+;-	-f (Eastin, et al. 1998)	-d (Eastin, et al. 1998)	nt
Coconut oil diethanolamine	68603-42-9	NE	Not Listed	-; ±;+;+ d (NTP 2001)	-;+	- d (Spalding, et al. 2000)	- d (Spalding, et al. 2000)	nt
Diethanolamine	111-42-2	3	Not Listed	-;-;+;+ d (NTP 1999h)	-;-	nt	- d (Spalding, et al. 2000)	nt
Ethyl Acrylate	140-88-5	2B	Delisted	+;+;+;+ g (NTP 1986a)	-;-	nt	- d (Nylander-French and French 1998;Tice, et al. 1997)	+ g (Yamamoto, et al. 1998b)
Furfuryl alcohol	98-00-0	NE	Not Listed	+; ±;+;- i (NTP 1999a)	-;-	nt	- d (Spalding, et al. 2000)	nt
Lauric acid diethanolamine	120-40-1	NE	Not Listed	-;-;-;+ d (NTP 1999b)	-;-	-f (Spalding, et al. 2000)	+ d (Spalding, et al. 2000)	nt
N-methyloacrylamide	924-42-5	3	Not Listed	-;-;+;+ g (NTP 1989b)	-;-	-g (Tennant, et al. 1995)	- d; - g (Eastin, et al. 1998)	nt
Methylphenidate	298-59-9	NE	Not Listed	-;-;+;+ f (NTP 1995a)	-;nt	-f (Tennant, et al. 1999)	- d (Tennant, et al. 1999)	nt
Pyridine	110-86-1	3	Not Listed	+;±;+;+ w (NTP 2000)	-;-	-g (Spalding, et al. 2000)	- d (Spalding, et al. 2000)	nt
Reserpine	50-55-5	3	Reasonable	+;-:+;+ f (NCI/NTP 1982a)	-;-	-f (Tennant, et al. 1995)	-d;-g (Tennant, et al. 1995)	- f (24)
Rotenone	83-79-4	NE	Not Listed	±;-;-;- f (NTP 1988b)	-;nt	- f (Eastin, et al. 1998)	+ d;- g (Eastin, et al. 1998)	- g (Yamamoto, et al. 1998b)

[1] "Probable" (2A) or "possible" (2B) human or "reasonably anticipated" to be a human carcinogen as identified by the International Agency for Research on Cancer (IARC) and/or NTP Report on Carcinogens (9th NTP ROC, revised January 2001), respectively.

Agent	CAS No.	IARC	NTP ROC	NCI/NTP Bioassays	Genotoxicity (Sal; Mn)	p53+/-	Tg.AC	RasH2
Resorcinol	108-46-3	3	Not Listed	-;-;-;- g (NTP 1992b)	-;+	- g (Eastin, et al. 1998)	+ d (Eastin, et al. 1998)	- g (Maronpot, et al. 2000)
Oleic acid diethanolamide	93-83-4	NE	Not Listed	-;-;-;- d (NTP 1999d)	-; nt	- d (Spalding, et al. 2000)	- d (Spalding, et al. 2000)	nt
Clolfibrate	637-07-0	3	Not Listed	nt	-;-	- g; - g (Storer, et al. 2001)	+d (Eastin, et al. 2001)	± g; + g (Usui, et al. 2001)
Dieldrin	60-57-1	3	Not Listed	-;-;±;- f (NCI/NTP 1978g)	-;nt	- f (Storer, et al. 2001)	nt	- f (Usui, et al. 2001)
Methapyrilene HCl	135-23-9	NE	Not Listed	+;+;nt;nt f (W Lijinsky 1080)	-;-	- g;-f (Storer, et al. 2001)	-d (Eastin, et al. 2001)	- g (Yamamoto, et al. 1996)
Haloperidol	52-86-8	NE	Not Listed	nt	nt;nt	- g (Storer, et al. 2001)	nt	- g (Usui, et al. 2001)
Chlorpromazine HCl	69-09-0	NE	Not Listed	nt	-;nt	- g;-g (Storer, et al. 2001)	nt	- g (Usui, et al. 2001)
Metaproterenol	586-06-1	NE	Not Listed	nt	nt;nt	- f;-f (Storer, et al. 2001)	nt	- f (24)
WY-14643	50892-23-4	NE	Not Listed	nt	nt;nt	- f (Storer, et al. 2001)	-d; ±f (Eastin, et al. 2001)	nt
Di(2-ethylhexyl)phthalate	117-81-7	3	Reasonable	+;+;+;+ f (NTP 1982)	-;-	± f (Storer, et al. 2001)	-d; -f (Eastin, et al. 2001)	+ (Usui, et al. 2001)
Sulfamethoxazole	723-46-6	3	Not Listed	nt	-;nt	- f (Storer, et al. 2001)	-d; -g (Eastin, et al. 2001)	-f (Usui, et al. 2001)
Sulfisoxazole	127-69-5	3	Not Listed	-;-;-l;- f (NCI/NTP 1979e)	-;nt	- f (Storer, et al. 2001)	- d;-g (Eastin, et al. 2001)	-f (Usui, et al. 2001)
Ampicillin	7177-48-2	3	Not Listed	±;-;-;- f (NTP 1987)	-;nt	- g (Storer, et al. 2001)	nt	-g (Usui, et al. 2001)
D-Mannitol	69-65-8	NE	Not Listed	-;-;-;- f (NCI/NTP 1982c)	-;-	-f (Storer, et al. 2001)	nt	- f (24)
1,1,2-Trichloroethane	79-00-5	3	Not Listed	-;-;+;+ g (NCI/NTP 1978a)	-;-	nt	nt	+ g (Yamamoto, et al. 1998b)
Xylenes (mixed)	1330-20-7	3	Not Listed	-;-;-;-;- g (NTP 1986c)	-;nt	nt	nt	- g (Yamamoto, et al. 1998b)
Furfural	98-01-1	3	Not Listed	+;-;+;+ g (NTP 1990b)	-;nt	nt	nt	+ g (Yamamoto, et al. 1998b)
5-Nitro-o-toluidine	99-55-8	3	Not Listed	-;-;+;+ f (NCI/NTP 19778)	+;nt	nt	nt	+f (Yamamoto, et al. 1998b)
Benzethonium chloride	121-54-0	NE	Not Listed	-;-;-;- d (NTP 1995b)	-;nt	nt	- d (Spalding, et al. 1999)	nt
o-Benzyl-*p*-chlorophenol	120-32-1	NE	Not Listed	-;±;+;- g (NTP 1994)	-;nt	nt	+ d (Spalding, et al. 1999)	nt

Agent	CAS No.	IARC	NTP ROC	NCI/NTP Bioassays	Genotoxicity (Sal; Mn)	p53+/-	Tg.AC	RasH2
2-Chloroethanol	107-07-3	NE	Not Listed	-;-;-;- d (NTP 1985a)	+;-	nt	- d (Spalding, et al. 1999)	nt
Phenol	108-95-2	3	Not Listed	-;-;-;- dw (NCI/NTP 1980)	-;+	nt	-d (Spalding, et al. 1999)	nt
Triethanolamine	102-71-6	3	Not Listed	±;-;ia;ia d (NTP 1999g)	-;-	nt	-d (Spalding, et al. 1999)	nt
Acetic anhydride	108-24-7	NE	Not Listed	nt	-;nt	nt	-d (Spalding, et al. 1999)	nt
2,4-dinitro-1-fluorobenzene	70-34-8	NE	Not Listed	nt	+;nt	nt	+d (Albert, et al. 1996)	nt
Diisopropylcarbodiimide	693-13-0	NE	Not Listed	in progress	-;+	in progress	+d (Spalding, et al. 1999)	nt
Dicyclohexylcarbodiimide	538-75-0	NE	Not Listed	In progress	+;+	nt	-d (Spalding, et al. 1999)	nt
Fluocinolone acetonide	67-73-2	NE	Not Listed	nt	nt;nt	nt	- d (Albert, et al. 1996)	nt
Tripropylene Glycol Diacrylate	42978-66-5	NE	Not Listed	nt	-;-	nt	+ d(Albert, et al. 1996)	nt
d-Limonene	5989-27-5	3	Not Listed	+'-;-;- f (NTP 1990a)	-;nt	- g (Carmichael, et al. 2000)	nt	nt
Foreign body (transponder)	NA	NE	Not Listed	nt	-;-	+ sc (Blanchard, et al. 1999)	- sc (French 2001)	nt
Acetone	67-64-1	NE	Not Listed	nt	-;-	nt	- d (Spalding, et al. 1999;Spalding, et al. 1993)	nt
Benzoyl peroxide	94-36-0	3	Not Listed	+ i-p[2] (NTP 1996)	-;nt	nt	+ d (Spalding, et al. 1993)	nt
Ethanol[3]	64-17-5	NE	Not Listed	in progress	-;nt	nt	- d (Spalding, et al. 1999)	nt
Methyl ethyl ketone peroxide	1338-23-4	NE	Not Listed	in progress	+;-	nt	+ d (Spalding, et al. 1993)	nt
4-Nitro-o-phenylenediamine	99-56-9	3	Not Listed	-;-;-;- f (NCI/NTP 1979b)	+; inc	nt	nt	± f (Yamamoto, et al. 1998b)
6-Nitrobenzimidazole	94-52-0	NE	Not Listed	-;-;+;+ f (NCI/NTP 1979c)	+;nt	nt	nt	- f (Yamamoto, et al. 1998b)

[2] Results from initiation-promotion studies in B6C3F1, Swiss (CD-1), and SENCAR mice (see reference 85).

Agent	CAS No.	IARC	NTP ROC	NCI/NTP Bioassays	Genotoxicity (Sal; Mn)	p53+/-	Tg.AC	RasH2
Cholestyramine	11041-12-6	NE	Not Listed	nt	nt; nt	nt	nt	- f (Yamamoto, et al. 1998b)
60 mHz Magnetic fields	NA	NE	Not Listed	-;-;-;-wb (NTP 1999c)	-;-	- wb (McCormick, et al. 1998)	- wb (McCormick, et al. 1998)	nt

Table 4. Summary performance of each strategy versus likely human cancer. All chemicals in Tables 1 and 2 are included as human carcinogens, but only those chemicals in Table 3 with negative NCI/NTP bioassay results are regarded as true human noncarcinogens.

Strategy	Positive for Carcinogens	Negative for Noncarcinogens	Positive for Noncarcinogens	Negative for Carcinogens	Overall Accuracy
(1) Trp53+/-	21	12	0	10	77 % (33/43)
(2) Trp53+/- (genotoxic)	16	5	0	4	84 % (21/25)
(3) Tg.AC	17	11	2	6	78 % (28/36)
(4) RasH2	21	9	0	7	81 % (30/37)
(5) Trp53+/- (genotoxic); RasH2 (nongenotoxic)	18	7	0	7	78 % (25/32)
(6) Trp53+/- (genotoxic); RasH2 (all)	31	7	0	5	88 % (38/43)
(7) Trp53+/- (genotoxic); Tg.AC (nongenotoxic)	21	9	0	6	83 % (30/36)
(8) Trp53+/- (genotoxic); Tg.AC for all	25	8	2	4	85 % (33/39)

Definitions

Positive for Carcinogens	=	Positive assay results for IARC/ROC carcinogens
Negative for Noncarcinogens	=	Negative assay results for IARC/ROC noncarcinogens
Positive for Noncarcinogens	=	Positive assay results for IARC/ROC noncarcinogens
Negative for Carcinogens	=	Negative assay results for IARC/ROC carcinogens

Table 5. Proportion of positive responses in the three transgenic models as a function of the IARC classification of these 99 chemicals.

IARC Classification	Trp53+/-	Tg.AC	RasH2	Overall
Group 1	83 % (10/12)	89 % (8/9)	57 % (4/7)[1]	79 % (22/28)
Group 2A	62 % (5/8)	50 % (2/4)	100 % (9/9)	76 % (16/21)
Group 2B[2]	55 % (6/11)	64 % (7/11)	69 % (9/13)	63 % (22/35)
Group 3	0 % (0/13)	21 % (3/14)	36 % (5/14)	20 % (8/41)
Not Evaluated	7 % (1/15)	29 % (7/24)	0 % (0/8)	17 % (8/47)

[1] Two of the three that were not positive were equivocal.

[2] Includes 7,12-dimethylbenzanthracene, 4-nitroquinoline N-oxide, and 4-hydroxyaminoquinoline-1-oxide.

Table 6. Summary of performance of each Strategy versus likely human cancer when all chemicals in Table 3 are regarded as true human non-carcinogens.

Strategy	Positive for Carcinogens	Negative for Noncarcinogens	Positive for Noncarcinogens	Negative for Carcinogens	Overall Accuracy
(1) Trp53+/-	21	27	1	10	81 % (48/59)
(2) Trp53+/- (genotoxic)	16	6	0	4	85 % (22/26)
(3) Tg.AC	17	29	10	6	74 % (44/62)
(4) RasH2	21	17	6	7	75 % (38/51)
(5) Trp53+/- (genotoxic); RasH2 (nongenotoxic)	18	17	1	7	81 % (35/43)
(6) Trp53+/- (genotoxic); RasH2 (all)	30	13	6	5	80 % (43/54)
(7) Trp53+/- (genotoxic); Tg.AC (nongenotoxic)	21	21	1	6	86 % (42/49)
(8) Trp53+/- (genotoxic); Tg.AC for all	25	20	10	5	75 % (45/60)
(9) NTP Rodent Bioassay	23	17	18	0	69 % (40/58)
(10) NTP Rat Bioassay; Tg.AC (nongenotoxic); Trp53+/- (genotoxic)	35	13	9	0	84 % (48/57)
(11) NTP Rat Bioassay; RasH2 (nongenotoxic); Trp53+/- (genotoxic)	33	11	8	0	85 % (44/52)
(12) NTP Rat Bioassay; genotoxicity	36	7	23	0	65 % (43/66)

Table 7. Summary performance of each strategy (vs. NTP rodent cancer results)

Strategy	Positive for Carcinogens	Negative for Noncarcinogens	Positive for Noncarcinogens	Negative for Carcinogens	Overall Accuracy
(1) Trp53+/-	7	12	0	16	54 % (19/35)
(2) Trp53+/- (genotoxic)	7	5	0	4	75 % (12/16)
(3) Tg.AC	14	10	2	14	60 % (24/40)
(4) RasH2	16	9	0	7	78 % (25/32)
(5) Trp53+/- (genotoxic); RasH2 (nongenotoxic)	9	10	0	7	73 % (19/26)
(6) Trp53+/- (genotoxic); RasH2 (all)	19	7	0	3	90 % (26/29)
(7) Trp53+/- (genotoxic); Tg.AC (nongenotoxic)	10	8	0	13	58 % (18/31)
(8) Trp53+/- (genotoxic); Tg.AC for all	15	7	2	12	61 % (22/36)

EXHIBIT 3

CONNETICS CORP

3400 W BAYSHORE RD
PALO ALTO, CA 94303
415. 843.2800

10-K/A

FORM 10-K/A
Filed on 03/29/2002 - Period: 12/31/2001
File Number 000-27406

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UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10–K/A

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE

SECURITIES EXCHANGE ACT OF 1934

For the Fiscal Year Ended December 31, 2001

Commission file number: 0–27406

Connetics Corporation

(Exact name of registrant as specified in its charter)

Delaware *(State or other jurisdiction of incorporation or organization)*	**94–3173928** *(I.R.S. Employer Identification No.)*
3290 West Bayshore Road **Palo Alto, California** *(Address of principal executive offices)*	**94303** *(zip code)*

Registrant's telephone number, including area code: (650) 843–2800

Securities registered pursuant to Section 12(b) of the Act: None

Securities registered pursuant to Section 12(g) of the Act:

Common Stock, $0.001 par value per share
Preferred Share Purchase Rights

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports) and (2) has been subject to such filing requirements for the past 90 days. Yes ☑ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S–K is not contained herein, and will not be contained to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10–K or any amendment to this Form 10–K. ☐

The aggregate market value of the voting stock held by non–affiliates of the registrant was approximately $225,516,073 as of March 22, 2002, based upon the closing sale price on the Nasdaq National Market reported for that date. The calculation excludes shares of common stock held by each officer and director and by each person who owns 5% or more of the outstanding common stock in that such persons may be deemed to be affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

There were 30,566,234 shares of registrant's common stock issued and outstanding as of March 22, 2002.

DOCUMENTS INCORPORATED BY REFERENCE

The information required by Part III of this Report, to the extent that it is not set forth in this Report, is incorporated by reference to the registrant's definitive proxy statement for the Annual Meeting of Stockholders to be held on May 16, 2002.

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FORWARD–LOOKING INFORMATION

Our disclosure and analysis in this Report, in other reports that we file with the Securities and Exchange Commission, in our press releases and in public statements of our officers contain forward–looking statements within the meaning of Section 27A of the Securities Act, and Section 21E of the Securities Exchange Act. Forward–looking statements give our current expectations or forecasts of future events. You can identify these statements by the fact that they do not relate strictly to historical or current events. They use words such as "anticipate," "estimate," "expect," "will," "may," "intend," "plan," "believe" and similar expressions in connection with discussion of future operating or financial performance. These include statements relating to future actions, prospective products or product approvals, future performance or results of current and anticipated products, sales efforts, expenses, the outcome of contingencies such as legal proceedings, and financial results.

Forward–looking statements may turn out to be wrong. They can be affected by inaccurate assumptions or by known or unknown risks and uncertainties. Many factors mentioned in this Report — for example, governmental regulation and competition in our industry — will be important in determining future results. No forward–looking statement can be guaranteed, and actual results may vary materially from those anticipated in any forward–looking statement.

Although we believe that our plans, intentions and expectations reflected in these forward–looking statements are reasonable, we may not achieve these plans, intentions or expectations. Forward–looking statements in this Report include, but are not limited to, those relating to the commercialization of our currently marketed products, the progress of our product development programs, developments with respect to clinical trials and the regulatory approval process, developments related to acquisitions and clinical development of drug candidates, and developments relating to the growth of our sales and marketing capabilities. Actual results, performance or achievements could differ materially from those contemplated, expressed or implied by the forward–looking statements contained in this Report. Important factors that could cause actual results to differ materially from our forward–looking statements are set forth in this Report. These factors are not intended to represent a complete list of the general or specific factors that may affect us. It should be recognized that other factors, including general economic factors and business strategies, and other factors not currently known to us, may be significant, presently or in the future, and the factors set forth in this Report may affect us to a greater extent than indicated. All forward–looking statements attributable to us or persons acting on our behalf are expressly qualified in their entirety by the cautionary statements set forth in this Report. Except as required by law, we do not undertake any obligation to update any forward–looking statement, whether as a result of new information, future events or otherwise.

PART I

Item 1. *Business*

The Company

References in this Report to "Connetics," "the Company," "we," "our" and "us" refer to Connetics Corporation, a Delaware corporation, and its consolidated subsidiaries. Our principal executive offices are located at 3290 West Bayshore Road, Palo Alto, CA 94303. Our telephone number is (650) 843–2800. Connetics®, Luxíq®, and OLUX® are registered trademarks, and Liquipatch™ and the seven interlocking "C's" design are trademarks, of Connetics. All other trademarks or service marks appearing in this Report are the property of their respective companies. We disclaim any proprietary interest in the marks and names of others.

Connetics is a specialty pharmaceutical company focusing exclusively on the treatment of dermatological conditions. We currently market two pharmaceutical products, Luxíq® Foam (betamethasone valerate), 0.12%, and OLUX® Foam (clobetasol propionate), 0.05%. Our commercial business is focused on the dermatology marketplace, which is characterized by a large patient population that is served by relatively small number of treating physicians. Our two dermatology products have clinically proven therapeutic

group of patients with a particular disease to obtain evidence of the agent's effectiveness against the targeted disease, to further explore risk and side effect issues, and to confirm preliminary data regarding optimal dosage ranges. Phase I and Phase II trials can sometimes be combined, with the FDA's concurrence, into a Phase I/II trial. Phase III trials involve more patients, and often more locations and clinical investigators than the earlier trials. At least one such trial is required for FDA approval to market a drug. Phase II and Phase III trials can sometimes be combined, with the FDA's concurrence, into a Phase II/III trial, which is an accelerated clinical trial intended to provide sufficient data for approval.

The rate of completion of our clinical trials depends upon, among other factors, the rate at which patients enroll in the study. Patient enrollment is a function of many factors, including the size of the patient population, the nature of the protocol, the proximity of patients to clinical sites and the eligibility criteria for the study. Delays in planned patient enrollment may result in increased costs and delays, which could have a material adverse effect on our business. In addition, side effects or adverse events that are reported during clinical trials can delay, impede, or prevent marketing approval.

Section 505(b)(2) of the Food, Drug and Cosmetic Act makes it possible for a company to possibly accelerate the FDA approval process. A so–called 505(b)(2) application permits a sponsor of a drug to satisfy the requirements for a full New Drug Application, or NDA, by relying on published studies or the FDA's findings of safety and effectiveness based on studies in a previously–approved NDA sponsored by another person, together with the studies generated on its own drug products. The FDA evaluates 505(b)(2) applications using the same standards of approval for an NDA, but the number of clinical trials required to support a 505(b)(2) application, and the amount of information in the application itself, may be substantially less than that required to support an NDA application. We used the 505(b)(2) application process for both Luxíq and OLUX, but the 505(b)(2) process may not be available for our other product candidates, and as a result the FDA process may be longer for those product candidates than it was for Luxíq and OLUX.

After we complete the clinical trials of a new drug product, we must file an NDA with the FDA. We must receive FDA clearance before we can commercialize the product, and the FDA may not grant approval on a timely basis or at all. The FDA can take between one and two years to review an NDA, and can take longer if significant questions arise during the review process. While various legislative and regulatory initiatives have focused on the need to reduce FDA review and approval times, the ultimate impact of such initiatives on our products cannot be certain. In addition, if there are changes in FDA policy while we are in product development, we may encounter delays or rejections that we did not anticipate when we submitted the new drug application or biologics license application for that product. We may not obtain regulatory approval for any products that we develop, even after committing such time and expenditures to the process. Even if regulatory approval of a product is granted, it may entail limitations on the indicated uses for which the product may be marketed.

Our products will also be subject to foreign regulatory requirements governing human clinical trials, manufacturing and marketing approval for pharmaceutical products. The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement are similar, but not identical, to FDA requirements, and they vary widely from country to country.

Manufacturing. The FDA regulates and inspects equipment, facilities, and processes used in the manufacturing of pharmaceutical products before providing approval to market a product. If after receiving clearance from the FDA, we make a material change in manufacturing equipment, location, or process, we may have to undergo additional regulatory review. We must apply to the FDA to change the manufacturer we use to produce any of our products. We and our contract manufacturers must adhere to current Good Manufacturing Practice and product–specific regulations enforced by the FDA through its facilities inspection program. The FDA also conducts regular, periodic visits to re–inspect equipment, facilities, and processes after the initial approval. If, as a result of these inspections, the FDA determines that our (or our contract manufacturers') equipment, facilities, or processes do not comply with applicable FDA regulations and conditions of product approval, the FDA may seek sanctions and/or remedies against us, including suspension of our manufacturing operations.

of our products on reasonable or acceptable terms. Any loss of a manufacturer or any difficulties that could arise in the manufacturing process could significantly affect our inventories and supply of products available for sale. If we are unable to supply sufficient amounts of our products on a timely basis, our market share could decrease and, correspondingly, our profitability could decrease.

If our contract manufacturers fail to comply with cGMP regulations, we may be unable to meet demand for our products and may lose potential revenue.

All of our contractors must comply with the applicable FDA cGMP regulations, which include quality control and quality assurance requirements as well as the corresponding maintenance of records and documentation. If Miza is not able to comply with the applicable cGMP regulations and other FDA regulatory requirements, our sales of marketed products could be reduced and we could suffer delays in the progress of clinical trials for products under development. We do not have control over our third–party manufacturers' compliance with these regulations and standards. The cGMP validation of a new facility and the approval of that manufacturer for a new drug product may take a year or more before manufacture can begin at the facility. Delays in obtaining FDA validation of a replacement manufacturing facility could cause an interruption in the supply of our products. Our business interruption insurance, which covers the loss of income for up to $8.0 million, may not completely mitigate the harm to our business from the interruption of the manufacturing of products caused by certain events, as the loss of a manufacturer could still have a negative effect on our sales, margins and market share, as well as our overall business and financial results.

If our supply of finished products is interrupted, our ability to maintain our inventory levels could suffer.

We try to maintain inventory levels that are no greater than necessary to meet our current projections. Any interruption in the supply of finished products could hinder our ability to timely distribute finished products. If we are unable to obtain adequate product supplies to satisfy our customers' orders, we may lose those orders and our customers may cancel other orders and stock and sell competing products. This in turn could cause a loss of our market share and negatively affect our revenues.

Supply interruptions may occur and our inventory may not always be adequate. Numerous factors could cause interruptions in the supply of our finished products including shortages in raw material required by our manufacturers, changes in our sources for manufacturing, our failure to timely locate and obtain replacement manufacturers as needed and conditions effecting the cost and availability of raw materials.

We cannot sell our current products and product candidates if we do not obtain and maintain governmental approvals.

Pharmaceutical companies are subject to heavy regulation by a number of national, state and local agencies. Of particular importance is the FDA in the United States. It has jurisdiction over all of our business and administers requirements covering testing, manufacture, safety, effectiveness, labeling, storage, record keeping, approval, advertising and promotion of our products. Failure to comply with applicable regulatory requirements could, among other things, result in fines; suspensions of regulatory approvals of products; product recalls; delays in product distribution, marketing and sale; and civil or criminal sanctions.

The process of obtaining and maintaining regulatory approvals for pharmaceutical products, and obtaining and maintaining regulatory approvals to market these products for new indications, is lengthy, expensive and uncertain. The manufacturing and marketing of drugs, including our products, are subject to continuing FDA and foreign regulatory review, and later discovery of previously unknown problems with a product, manufacturing process or facility may result in restrictions, including withdrawal of the product from the market. The FDA is permitted to revisit and change its prior determinations and it may change its position with regard to the safety or effectiveness of our products. Even if the FDA approves our products, the FDA is authorized to impose post–marketing requirements such as:

- testing and surveillance to monitor the product and its continued compliance with regulatory requirements,

- submitting products for inspection and, if any inspection reveals that the product is not in compliance, the prohibition of the sale of all products from the same lot,
- suspending manufacturing,
- recalling products, and
- withdrawing marketing clearance.

Even before any formal regulatory action, we could voluntarily decide to cease distribution and sale or recall any of our products if concerns about the safety or effectiveness develop.

To market our products in countries outside of the United States, we and our partners must obtain similar approvals from foreign regulatory bodies. The foreign regulatory approval process includes all of the risks associated with obtaining FDA approval, and approval by the FDA does not ensure approval by the regulatory authorities of any other country.

In its regulation of advertising, the FDA from time to time issues correspondence to pharmaceutical companies alleging that some advertising or promotional practices are false, misleading or deceptive. The FDA has the power to impose a wide array of sanctions on companies for such advertising practices, and the receipt of correspondence from the FDA alleging these practices can result in the following:

- incurring substantial expenses, including fines, penalties, legal fees and costs to comply with the FDA's requirements,
- changes in the methods of marketing and selling products,
- taking FDA–mandated corrective action, which may include placing advertisements or sending letters to physicians rescinding previous advertisements or promotion, and
- disruption in the distribution of products and loss of sales until compliance with the FDA's position is obtained.

In recent years, various legislative proposals have been offered in Congress and in some state legislatures that include major changes in the health care system. These proposals have included price or patient reimbursement constraints on medicines and restrictions on access to certain products. We cannot predict the outcome of such initiatives, and it is difficult to predict the future impact of the broad and expanding legislative and regulatory requirements affecting us.

We may spend a significant amount of money to obtain FDA and other regulatory approvals, which may never be granted.

Successful product development in our industry is highly uncertain, and the process of obtaining FDA and other regulatory approvals is lengthy and expensive. Very few research and development projects produce a commercial product. Product candidates that appear promising in the early phases of development may fail to reach the market for a number of reasons, including that the product candidate did not demonstrate acceptable clinical trial results even though it demonstrated positive preclinical trial results, or that the product candidate was not effective in treating a specified condition or illness, or that the FDA did not approve our product candidate for its intended use.

To obtain approval, we must show in preclinical and clinical trials that our products are safe and effective, and the marketing and manufacturing of pharmaceutical products are subject to rigorous testing procedures. The FDA approval processes require substantial time and effort, the FDA continues to modify product development guidelines, and the FDA may not grant approval on a timely basis or at all. Clinical trial data can be the subject of differing interpretation, and the FDA has substantial discretion in the approval process. The FDA may not interpret our clinical data the way we do. The FDA may also require additional clinical data to support approval. The FDA can take between one and two years to review new drug applications, or longer if significant questions arise during the review process. We may not be able to obtain FDA approval to conduct clinical trials or to manufacture and market any of the products we develop, acquire or license. Moreover, the

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SFAS 142. In July 2001, the FASB issued SFAS No. 142, "Goodwill and Other Intangible Assets" (SFAS 142), which addresses the financial accounting and reporting for acquired goodwill and other intangible assets. Under SFAS 142, we are no longer required to amortize goodwill and intangible assets with indefinite lives, but will be required to periodically review these for impairment. Intangible assets determined to have definitive lives will continue to be amortized over their useful lives. SFAS 142 is effective for years ending after December 15, 2001. We adopted SFAS 142 effective January 1, 2002, and reclassified amounts to goodwill that were previously allocated to assembled workforce. Upon adoption, we ceased the amortization of goodwill currently representing expense of $0.7 million per year. Although we have not completed the transactional impairment test, we currently do not expect the results of such test to have a material effect on our financial position or results of operations.

SFAS 144. In October 2001, the FASB issued SFAS No. 144, "Accounting for the Impairment or Disposal of Long–Lived Assets" (SFAS 144), which establishes a single accounting model for the impairment or disposal of long–lived assets, including discontinued operations. SFAS 144 supersedes SFAS 121, "Accounting for the Impairment of Long–Lived Assets and for Long–Lived Assets to be Disposed Of." SFAS 144 requires that long–lived assets to be disposed of by sale be measured at the lower of carrying amount or fair value less cost to sell, whether reported in continuing operations or in discontinued operations. SFAS 144 excludes from the definition of long–lived assets goodwill and other intangibles that are not amortized in accordance with SFAS 142. SFAS 144 also expands the reporting of discontinued operations to include components of an entity that have been or will be disposed of rather than limiting such discontinuance to a segment of a business. SFAS 144 is effective for years ending after December 15, 2001. We adopted SFAS 144 effective January 1, 2002, and it did not have a significant impact on our financial position or results of operations.

Factors That May Affect Forward–Looking Statements

A wide range of factors could materially affect our future developments and performance, including the following:

- We have experienced operating losses every year since our incorporation and expect to incur additional losses for at least the next few years. Losses are expected to fluctuate from period to period based on timing of product revenues, clinical material purchases, possible acquisitions of new products and technologies, scale–up activities and clinical activities. Therefore, the time for us to reach profitability is uncertain and we may never be able to generate revenue from our products now under development or achieve profitability on a sustained basis.

- There are risks related to the management of the marketing and sales of our products. Our success depends in part on our ability to effectively manage the distribution of our products and to market and sell our products successfully. If Luxíq and OLUX do not sustain market acceptance, our financial condition and results of operations will be adversely affected. Future revenues from sales are uncertain as we are subject to patent risks and competition from new products.

- We do not have manufacturing capabilities, and we receive all of our products (including clinical trial material) from contract manufacturing companies. We currently have no manufacturing facilities nor do we intend to develop such capabilities in the near future. If any of our contract manufacturers were to fail to provide product to us on a timely basis, we might have to delay clinical trials or commercial sales, which would have a material adverse effect on our results of operations.

- We are subject to uncertainties associated with product development and market acceptance. We have several product candidates in clinical or preclinical development. Products under development may not be safe and effective or approved by the FDA, or we may not be able to produce them in commercial quantities at reasonable costs, and the products may not gain satisfactory market acceptance.

- Our future capital uses and requirements depend on numerous factors, including costs associated with the research, development, clinical testing and obtaining regulatory approvals of products in our pipeline; enforcing patent claims and intellectual property rights; acquisition of new products and

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SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

CONNETICS CORPORATION
a Delaware corporation

By: /s/ JOHN L. HIGGINS

John L. Higgins
Chief Financial Officer
Executive Vice President, Finance and Corporate Development

Date: March 29, 2002

Pursuant to the requirements of the Securities Exchange Act of 1934, this Report has been signed below by the following persons in the capacities and on the dates indicated.

Signature	Title	Date
Principal Executive Officer:		
/s/ THOMAS G. WIGGANS Thomas G. Wiggans	President, Chief Executive Officer and Director	March 29, 2002
Principal Financial and Accounting Officer:		
/s/ JOHN L. HIGGINS John L. Higgins	Chief Financial Officer; Executive Vice President, Finance and Corporate Development	March 29, 2002
Directors:		
/s/ ALEXANDER E. BARKAS Alexander E. Barkas	Director	March 29, 2002
/s/ EUGENE A. BAUER Eugene A. Bauer	Director	March 29, 2002
/s/ JOHN C. KANE John C. Kane	Director	March 29, 2002
/s/ THOMAS D. KILEY Thomas D. Kiley	Director	March 29, 2002
/s/ GLENN A. OCLASSEN Glenn A. Oclassen	Director	March 29, 2002
/s/ LEON E. PANETTA Leon E. Panetta	Director	March 29, 2002
/s/ G. KIRK RAAB G. Kirk Raab	Chairman of the Board, Director	March 29, 2002

EXHIBIT 4

CONNETICS CORP

3400 W BAYSHORE RD
PALO ALTO, CA 94303
415. 843.2800

10-K/A

FORM 10-K/A
Filed on 12/02/2003 – Period: 12/31/2002
File Number 000-27406

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 10–K/A

(Amendment No. 2)
ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the Fiscal Year Ended December 31, 2002

Commission file number: 0–27406

CONNETICS CORPORATION

(Exact name of registrant as specified in its charter)

Delaware *(State or other jurisdiction of incorporation or organization)*	**94–3173928** *(I.R.S. Employer Identification No.)*
3290 West Bayshore Road **Palo Alto, California** *(Address of principal executive offices)*	**94303** *(zip code)*

Registrant's telephone number, including area code: **(650) 843–2800**

Securities registered pursuant to Section 12(b) of the Act: **None**

Securities registered pursuant to Section 12(g) of the Act:

Common Stock, $0.001 par value per share
Preferred Share Purchase Rights

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports) and (2) has been subject to such filing requirements for the past 90 days. YES ☒ NO ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S–K is not contained herein, and will not be contained to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10–K or any amendment to this Form 10–K. ☒

Indicate by check mark whether the registrant is an accelerated filer (as defined in Exchange Act Rule 12b–2). YES ☒ NO ☐

The aggregate market value of the voting stock held by non–affiliates of the registrant was approximately $250,191,000 as of June 28, 2002, based upon the shares outstanding and the closing sale price on the Nasdaq National Market reported for that date. The calculation excludes shares of common stock held by each officer and director and by each person known by the registrant to beneficially own 5% or more of the outstanding common stock in that such persons may be deemed to be affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

There were 31,398,567 shares of registrant's common stock issued and outstanding as of March 3, 2003.

DOCUMENTS INCORPORATED BY REFERENCE

The information required by Part III of this Report, to the extent that it is not set forth in this Report, is incorporated by reference to the registrant's definitive proxy statement for the Annual Meeting of Stockholders to be held on May 14, 2003.

effects associated with increasing doses. Phase II trials generally involve administration of a product to a larger group of patients with a particular disease to obtain evidence of the agent's effectiveness against the targeted disease, to further explore risk and side effect issues, and to confirm preliminary data regarding optimal dosage ranges. Phase III trials involve more patients, and often more locations and clinical investigators than the earlier trials. At least one such trial is required for FDA approval to market a drug.

The rate of completion of our clinical trials depends upon, among other factors, the rate at which patients enroll in the study. Patient enrollment is a function of many factors, including the size of the patient population, the nature of the protocol, the proximity of patients to clinical sites and the eligibility criteria for the study. Delays in planned patient enrollment may result in increased costs and delays, which could have a material adverse effect on our business. In addition, side effects or adverse events that are reported during clinical trials can delay, impede, or prevent marketing approval.

The Food, Drug and Cosmetic Act includes provisions for accelerating the FDA approval process under certain circumstances. For example, we used the so–called 505(b)(2) application process for both OLUX and Luxíq, which permitted us to satisfy the requirements for a full NDA by relying on published studies or the FDA's findings of safety and effectiveness based on studies in a previously–approved NDA sponsored by another applicant, together with the studies generated on our products. While the FDA evaluation used the same standards of approval as an NDA, the number of clinical trials required to support a 505(b)(2) application, and the amount of information in the application itself, may be substantially less than that required to support an NDA application. The 505(b)(2) process will not be available for all of our other product candidates, and as a result the FDA process may be longer for those product candidates than it was for OLUX and Luxíq.

After we complete the clinical trials of a new drug product, we must file an NDA with the FDA. We must receive FDA clearance before we can commercialize the product, and the FDA may not grant approval on a timely basis or at all. The FDA can take between one and two years to review an NDA, and can take longer if significant questions arise during the review process. In addition, if there are changes in FDA policy while we are in product development, we may encounter delays or rejections that we did not anticipate when we submitted the new drug application for that product. We may not obtain regulatory approval for any products that we develop, even after committing such time and expenditures to the process. Even if regulatory approval of a product is granted, it may entail limitations on the indicated uses for which the product may be marketed.

Our products will also be subject to foreign regulatory requirements governing human clinical trials, manufacturing and marketing approval for pharmaceutical products. The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement are similar, but not identical, to FDA requirements, and they vary widely from country to country.

Manufacturing. The FDA regulates and inspects equipment, facilities, and processes used in the manufacturing of pharmaceutical products before providing approval to market a product. If after receiving clearance from the FDA, we make a material change in manufacturing equipment, location, or process, we may have to undergo additional regulatory review. We must apply to the FDA to change the manufacturer we use to produce any of our products. We and our contract manufacturers must adhere to cGMP and product–specific regulations enforced by the FDA through its facilities inspection program. The FDA also conducts regular, periodic visits to re–inspect equipment, facilities, and processes after the initial approval. If, as a result of these inspections, the FDA determines that our (or our contract manufacturers') equipment, facilities, or processes do not comply with applicable FDA regulations and conditions of product approval, the FDA may seek sanctions and/or remedies against us, including suspension of our manufacturing operations.

Post–Approval Regulation. The FDA continues to review marketed products even after granting regulatory clearances, and if previously unknown problems are discovered or if we fail to comply with the applicable regulatory requirements, the FDA may restrict the marketing of a product or impose the withdrawal of the product from the market, recalls, seizures, injunctions or criminal sanctions. In its regulation of advertising, the FDA from time to time issues correspondence to pharmaceutical companies alleging that

We cannot sell our current products and product candidates if we do not obtain and maintain governmental approvals.

Pharmaceutical companies are subject to heavy regulation by a number of national, state and local agencies. Of particular importance is the FDA in the United States. It has jurisdiction over all of our business and administers requirements covering testing, manufacture, safety, effectiveness, labeling, storage, record keeping, approval, advertising and promotion of our products. Failure to comply with applicable regulatory requirements could, among other things, result in fines; suspensions of regulatory approvals of products; product recalls; delays in product distribution, marketing and sale; and civil or criminal sanctions.

The process of obtaining and maintaining regulatory approvals for pharmaceutical products, and obtaining and maintaining regulatory approvals to market these products for new indications, is lengthy, expensive and uncertain. The manufacturing and marketing of drugs, including our products, are subject to continuing FDA and foreign regulatory review, and later discovery of previously unknown problems with a product, manufacturing process or facility may result in restrictions, including withdrawal of the product from the market. The FDA is permitted to revisit and change its prior determinations and it may change its position with regard to the safety or effectiveness of our products. Even if the FDA approves our products, the FDA is authorized to impose post–marketing requirements such as:

- testing and surveillance to monitor the product and its continued compliance with regulatory requirements,
- submitting products for inspection and, if any inspection reveals that the product is not in compliance, the prohibition of the sale of all products from the same lot,
- suspending manufacturing,
- recalling products, and
- withdrawing marketing approval.

Even before any formal regulatory action, we could voluntarily decide to cease distribution and sale or recall any of our products if concerns about the safety or effectiveness develop.

To market our products in countries outside of the United States, we and our partners must obtain similar approvals from foreign regulatory bodies. The foreign regulatory approval process includes all of the risks associated with obtaining FDA approval, and approval by the FDA does not ensure approval by the regulatory authorities of any other country.

In its regulation of advertising, the FDA from time to time issues correspondence to pharmaceutical companies alleging that some advertising or promotional practices are false, misleading or deceptive. The FDA has the power to impose a wide array of sanctions on companies for such advertising practices, and the receipt of correspondence from the FDA alleging these practices can result in the following:

- incurring substantial expenses, including fines, penalties, legal fees and costs to comply with the FDA's requirements,
- changes in the methods of marketing and selling products,
- taking FDA–mandated corrective action, which may include placing advertisements or sending letters to physicians rescinding previous advertisements or promotion, and
- disruption in the distribution of products and loss of sales until compliance with the FDA's position is obtained.

In recent years, various legislative proposals have been offered in Congress and in some state legislatures that include major changes in the health care system. These proposals have included price or patient reimbursement constraints on medicines and restrictions on access to certain products. We cannot predict the outcome of such initiatives, and it is difficult to predict the future impact of the broad and expanding legislative and regulatory requirements affecting us.

We may spend a significant amount of money to obtain FDA and other regulatory approvals, which may never be granted. Failure to obtain such regulatory approvals could adversely affect our prospects for future revenue growth.

Successful product development in our industry is highly uncertain, and the process of obtaining FDA and other regulatory approvals is lengthy and expensive. Very few research and development projects produce a commercial product. Product candidates that appear promising in the early phases of development may fail to reach the market for a number of reasons, including that the product candidate did not demonstrate acceptable clinical trial results even though it demonstrated positive preclinical trial results, or that the product candidate was not effective in treating a specified condition or illness, or that the FDA did not approve our product candidate for its intended use.

To obtain approval, we must show in preclinical and clinical trials that our products are safe and effective. The FDA approval processes require substantial time and effort, the FDA continues to modify product development guidelines, and the FDA may not grant approval on a timely basis or at all. Clinical trial data can be the subject of differing interpretation, and the FDA has substantial discretion in the approval process. The FDA may not interpret our clinical data the way we do. The FDA may also require additional clinical data to support approval. The FDA can take between one and two years to review new drug applications, or longer if significant questions arise during the review process. We may not be able to obtain FDA approval to conduct clinical trials or to manufacture and market any of the products we develop, acquire or license. Moreover, the costs to obtain approvals could be considerable and the failure to obtain or delays in obtaining an approval could have a significant negative effect on our business.

If OLUX and Luxíq do not sustain market acceptance, our revenues will not be predictable and may not cover our operating expenses.

Our future revenues will depend upon dermatologist and patient acceptance of OLUX and Luxíq. Factors that could affect acceptance of OLUX and Luxíq include:

- satisfaction with existing alternative therapies,
- the effectiveness of our sales and marketing efforts,
- the cost of the product as compared with alternative therapies, and
- undesirable and unforeseeable side effects.

We cannot predict the potential long–term patient acceptance of, or the effects of competition and managed health care on, sales of either product.

We rely on third parties to conduct clinical trials for our products, and those third parties may not perform satisfactorily. Failure of those third parties to perform satisfactorily may significantly delay commercialization of our products, increase expenditures and negatively affect our prospects for future revenue growth.

We do not have the ability to independently conduct clinical studies, and we rely on third parties to perform this function. If these third parties do not perform satisfactorily, we may not be able to locate acceptable replacements or enter into favorable agreements with them, if at all. If we are unable to rely on clinical data collected by others, we could be required to repeat, extend the duration of, or increase the size of, clinical trials, which could significantly delay commercialization and require significantly greater expenditures.

If we are unable to develop new products, our expenses may continue to exceed our revenue indefinitely, without any return on the investment.

We currently have a variety of new products in various stages of research and development and are working on possible improvements, extensions and reformulations of some existing products. These research and development activities, as well as the clinical testing and regulatory approval process, which must be completed before commercial quantities of these developments can be sold, will require significant commitments of personnel and financial resources. Delays in the research, development, testing or approval processes will cause a corresponding delay in revenue generation from those products.

We re–evaluate our research and development efforts regularly to assess whether our efforts to develop a particular product or technology are progressing at a rate that justifies our continued expenditures. On the basis of these re–evaluations, we have abandoned in the past, and may abandon in the future, our efforts on a particular product or technology. Products we are researching or developing may never be successfully released to the market and, regardless of whether they are ever released to the market, the expense of such processes will have already been incurred.

If we do not successfully integrate new products into our business, we may not be able to sustain revenue growth and we may not be able to compete effectively.

When we acquire or develop new products and product lines, we must be able to integrate those products and product lines into our systems for marketing, sales and distribution. If these products or product lines are not integrated successfully, the potential for growth is limited. The new products we acquire or develop could have channels of distribution, competition, price limitations or marketing acceptance different from our current products. As a result, we do not know whether we will be able to compete effectively and obtain market acceptance in any new product categories. A new product may require us to significantly increase our sales force and incur additional marketing, distribution and other operational expenses. These additional expenses could negatively affect our gross margins and operating results. In addition, many of these expenses could be incurred prior to the actual distribution of new products. Because of this timing, if the new products are not accepted by the market, or if they are not competitive with similar products distributed by others, the ultimate success of the acquisition or development could be substantially diminished.

We rely on the services of a single company to distribute our products to our customers. A delay or interruption in the distribution of our products could negatively impact our business.

All of our product distribution activities are handled by SPS. SPS stores and distributes our products from a warehouse in Tennessee. Any delay or interruption in the process or in payment could result in a delay delivering product to our customers, which could have a material effect on our business.

Our sales depend on payment and reimbursement from third party payors, and if they reduce or refuse payment or reimbursement, the use and sales of our products will suffer, we may not increase our market share, and our revenues and profitability will suffer.

Our products' commercial success is dependent, in part, on whether third–party reimbursement is available for the use of our products by hospitals, clinics, doctors and patients. Third–party payors include state and federal governments, under programs such as Medicare and Medicaid, managed care organizations, private insurance plans and health maintenance organizations. Over 70% of the U.S. population now participates in some version of managed care. Because of the size of the patient population covered by managed care organizations, it is important to our business that we market our products to them and to the pharmacy benefit managers that serve many of these organizations. Payment or reimbursement of only a portion of the cost of our prescription products could make our products less attractive, from a net–cost perspective, to patients, suppliers and prescribing physicians. Managed care organizations and other third–party payors try to negotiate the pricing of medical services and products to control their costs. Managed care organizations and pharmacy benefit managers typically develop formularies to reduce their cost for medications. Formularies can be based on the prices and therapeutic benefits of the available products. Due to their lower costs, generics are often favored. The breadth of the products covered by formularies varies considerably from one managed care organization to another, and many formularies include alternative and competitive products for treatment of particular medical conditions. Exclusion of a product from a formulary can lead to its sharply reduced usage in the managed care organization patient population. If our products are not included within an adequate number of formularies or adequate reimbursement levels are not provided, or if those policies increasingly favor generic products, our market share and gross margins could be negatively affected, as could our overall business and financial condition.

To the extent that our products are purchased by patients through a managed care group with which we have a

The decrease in license revenue in 2001 from 2000 was in part due to our decision in May 2001 to reduce our investment in the development of relaxin. Through the end of 2002, we had not entered into any new licensing opportunities or other strategic alternatives for relaxin. Effective April 1, 2000 we assigned to InterMune our remaining rights and obligations under a license with Genentech for Actimmune and the corresponding supply agreement. In exchange, InterMune paid us approximately $5.2 million in 2000. InterMune paid an additional $942,000 by the end of March 2001, which was offset by related product rebates and chargebacks of $171,000. In August 2002, we entered into an agreement with InterMune to terminate our exclusive option for certain rights in the dermatology field in exchange for an up–front, non–refundable payment of $350,000. We recognized the full amount of this revenue in 2002.

We anticipate that product revenue will increase in 2003 due to continued sales growth of OLUX and Luxíq. We also anticipate that license and contract revenue will decrease, as several revenue streams from 2002 will not recur in 2003, while royalty revenue is expected to remain about the same in 2003. Beyond 2003, we expect license revenue to fluctuate significantly depending on whether we enter into additional collaborations, when and whether we or our partners achieve milestones under existing agreements, and the timing of any new business opportunities that we may identify.

Cost of Product Revenues

Our cost of product revenues includes the third party costs of manufacturing OLUX, Luxíq, Ridaura (until April 2001), and Actimmune (until April 2000), royalty payments based on a percentage of our product revenues and product freight and distribution costs from SPS, the third party that handles all of our product distribution activities. We recorded cost of product revenues of $4.2 million in 2002 compared to $3.1 million in 2001 and $3.9 million in 2000. The increase in total cost of product revenues in 2002 was the result of an increase in sales volumes. On a percentage basis, cost of product revenues decreased to 8.8% in 2002 from 10.1% in 2001. When we acquired Connetics Australia, we began to eliminate all intercompany transactions in consolidation, which included our royalty expense and Connetics Australia's related royalty income. The decrease in cost of product revenues from 2001 to 2002 on a percentage basis was primarily due to the elimination of intercompany royalties of $1.7 million, partially offset by an average increase in the cost per unit of our products of approximately 6%. The decrease in cost of product revenues from 2000 to 2001 was primarily due to the elimination of intercompany royalties of $1.6 million, as well as a change in product mix as a result of discontinuing sales of Ridaura, which had higher manufacturing costs than our other products. We sold the rights to Ridaura to Prometheus in April 2001. We anticipate a slight increase in the cost of product revenues in 2003, on a per unit basis as we shift the production of our products to domestic suppliers.

Research and Development

Research and development expenses include costs of personnel to support our research and development activities, costs of preclinical studies, costs of conducting our clinical trials, such as clinical investigator fees, monitoring costs, data management and drug supply costs, external research programs, and an allocation of facilities costs, salaries and benefits, and overhead costs such as rent, supplies and utilities. Research and development expenses increased in 2002 to $25.8 million, compared to $19.2 million in 2001 and $21.9 million in 2000.

In 2002, our research and development expenses primarily consisted of:

- $7.4 million on preclinical and clinical research in the development of new dermatology products,
- $5.1 million on quality assurance and quality control in the enhancement of existing dermatology products,
- $3.9 million on the optimization of manufacturing and process development for existing dermatology products,
- $2.7 million on manufacturing, process development and optimization of dermatology products under development,

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SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Connetics Corporation
a Delaware corporation

By: /s/ JOHN L. HIGGINS

John L. Higgins
Chief Financial Officer
Executive Vice President, Finance
and Corporate Development

Date: December 2, 2003

EXHIBIT 5

CONNETICS CORP

3400 W BAYSHORE RD
PALO ALTO, CA 94303
415. 843.2800

10–K

FORM 10–K
Filed on 03/15/2004 – Period: 12/31/2003
File Number 000–27406

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10–K

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d)
OF THE SECURITIES EXCHANGE ACT OF 1934

For the Fiscal Year Ended December 31, 2003

Commission File Number 0–27406

CONNETICS CORPORATION

(Exact name of registrant as specified in its charter)

Delaware *(State or other jurisdiction of incorporation or organization)*	**94–3173928** *(I.R.S. Employer Identification No.)*
3290 West Bayshore Road **Palo Alto, California** *(Address of principal executive offices)*	**94303** *(zip code)*

Registrant's telephone number, including area code: **(650) 843–2800**
Securities registered pursuant to Section 12(b) of the Act: **None**
Securities registered pursuant to Section 12(g) of the Act:

Common Stock, $0.001 par value per share
Preferred Share Purchase Rights

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports) and (2) has been subject to such filing requirements for the past 90 days. YES ☒ NO☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S–K is not contained herein, and will not be contained to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10–K or any amendment to this Form 10–K. ☒

Indicate by check mark whether the registrant is an accelerated filer (as defined in Exchange Act Rule 12b–2). YES ☒ NO ☐

The aggregate market value of the voting stock held by non–affiliates of the registrant was approximately $371,000,000 as of June 30, 2003, based upon the shares outstanding and the closing sale price on the Nasdaq National Market reported for that date. The calculation excludes shares of common stock held by each officer and director and by each person known by the registrant to beneficially own 5% or more of the outstanding common stock as of that date, in that such persons may be deemed to be affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

There were 35,202,167 shares of registrant's common stock issued and outstanding as of March 9, 2004.

DOCUMENTS INCORPORATED BY REFERENCE

The information required by Part III of this Report, to the extent that it is not set forth in this Report, is incorporated by reference to the registrant's definitive proxy statement for the Annual Meeting of Stockholders to be held on May 7, 2004.

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Forward–Looking Statements

Our disclosure and analysis in this Report, in other reports that we file with the Securities and Exchange Commission, in our press releases and in public statements of our officers contain forward–looking statements within the meaning of Section 27A of the Securities Act of 1933, and Section 21E of the Securities Exchange Act of 1934. Forward–looking statements give our current expectations or forecasts of future events. Forward–looking statements may turn out to be wrong. They can be affected by inaccurate assumptions or by known or unknown risks and uncertainties. Many factors mentioned in this Report — for example, governmental regulation and competition in our industry — will be important in determining future results. No forward–looking statement can be guaranteed, and actual results may vary materially from those anticipated in any forward–looking statement.

You can identify forward–looking statements by the fact that they do not relate strictly to historical or current events. They use words such as "anticipate," "estimate," "expect," "will," "may," "intend," "plan," "believe" and similar expressions in connection with discussion of future operating or financial performance. These include statements relating to future actions, prospective products or product approvals, future performance or results of current and anticipated products, sales efforts, expenses, the outcome of contingencies such as legal proceedings, and financial results.

Although we believe that our plans, intentions and expectations reflected in these forward–looking statements are reasonable, we may not achieve these plans, intentions or expectations. Forward–looking statements in this Report include, but are not limited to, those relating to the commercialization of our currently marketed products, the progress of our product development programs, developments with respect to clinical trials and the regulatory approval process, developments related to acquisitions, and developments relating to our sales and marketing capabilities. Actual results, performance or achievements could differ materially from those contemplated, expressed or implied by the forward–looking statements contained in this Report. In particular, this Report sets forth important factors that could cause actual results to differ materially from our forward–looking statements. These factors are not intended to represent a complete list of the general or specific factors that may affect us. It should be recognized that other factors, including general economic factors and business strategies, and other factors not currently known to us, may be significant, now or in the future, and the factors set forth in this Report may affect us to a greater extent than indicated. All forward–looking statements attributable to us or persons acting on our behalf are expressly qualified in their entirety by the cautionary statements set forth in this Report. Except as required by law, we do not undertake any obligation to update any forward–looking statement, whether as a result of new information, future events or otherwise.

PART I

Item 1. Business

THE COMPANY

References in this Report to "Connetics," "the Company," "we," "our" and "us" refer to Connetics Corporation, a Delaware corporation, and its consolidated subsidiaries. Unless the context specifically requires otherwise, "we" includes Connetics Australia Pty Ltd. Connetics was incorporated in Delaware in February 1993, and our principal executive offices are located at 3290 West Bayshore Road, Palo Alto, California 94303. Our telephone number is (650) 843–2800. Connetics®, Luxíq®, OLUX® and Extina® are registered trademarks, and VersaFoam™, Actiza™, Liquipatch™, and the seven interlocking "C's" design are trademarks, of Connetics. Velac® is a registered trademark of Yamanouchi Europe B.V. Soriatane® is a registered trademark of Hoffmann–La Roche Inc., and was assigned to us effective March 4, 2004. All other trademarks or service marks appearing in this Report are the property

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OUR PRODUCTS

OLUX Foam

OLUX is a foam formulation of clobetasol propionate, one of the most widely prescribed super high–potency topical steroids. OLUX has been proven to deliver rapid and effective results for scalp and non–scalp psoriasis. In fact, according to Physician Global Assessments, significantly more patients were completely clear or almost clear after two weeks of treatment. Topical steroids are used to treat a range of dermatoses, for which approximately 24 million steroid prescriptions are written annually. In 2003, OLUX and Luxíq comprised 7.3% of the branded prescriptions in these combined topical steroid markets, corresponding to 17% of the retail annual branded sales for 2003. While the topical steroid market is highly fragmented, we believe that OLUX is the number one branded super–high potency topical steroid prescribed by U.S. dermatologists.

We began selling OLUX in November 2000 for the short–term, topical treatment of inflammatory and pruritic manifestations of moderate to severe corticosteroid–responsive scalp dermatoses. In December 2002, the FDA approved our supplemental New Drug Application, or sNDA, to market OLUX for the treatment of mild to moderate non–scalp psoriasis.

A study conducted at Stanford University School of Medicine compared the safety and effectiveness, patient satisfaction, quality of life, and cost–effectiveness of two clobetasol regimens in the treatment of psoriasis. In a single–blind design, 29 patients were randomized to receive either clobetasol foam on the skin and scalp or a combination of clobetasol cream on the skin and lotion on the scalp for 14 days. Severity of disease and quality of life were evaluated using several tools, including the Psoriasis Area Severity Index, or PASI, and the Dermatology Life Quality Index. The trial showed that the increased improvement in clinical severity, decreased application time, and increased perception of relative efficacy, combined with similar cost of treatment, suggest that OLUX is a better choice than cream and lotion for some patients. This study supports our belief that improved patient compliance with the foam will yield better treatment results than the same active ingredient in other formulations.

Mipharm S.p.A., which holds a license to market OLUX in Italy, filed a Marketing Authorization Application, or MAA, in 2002 for OLUX with the Medicines and Healthcare Products Regulatory Agency, known as MHRA, in the United Kingdom. The MHRA granted marketing authorization for OLUX in June 2003. The approval grants the right to market and launch OLUX in the U.K. Following MHRA approval, updated MAAs were submitted to each of the EU Concerned Member States, using a process called the mutual recognition process, or MRP. The MRP was completed in December 2003 with all Concerned Member States granting approval for OLUX except France. National licenses are expected to be issued in the first half of 2004. We will receive milestone payments and royalties from Mipharm on future product sales in the Italian territory. We retain marketing and distribution rights for the rest of Europe and are seeking commercial partners outside the territory licensed to Mipharm. We have signed a letter of intent with a third party for rights to market OLUX in all of Europe excluding the U.K. and the territory licensed to Mipharm.

Luxíq Foam

Luxíq is a foam formulation of betamethasone valerate, a mid–potency topical steroid prescribed for the treatment of mild–to–moderate steroid–responsive scalp dermatoses such as psoriasis, eczema and seborrheic dermatitis. We have been selling Luxíq commercially in the United States since 1999. In a clinical trial, a majority of patients were judged to be almost clear or completely clear (90–100%) of scalp psoriasis at the end of treatment as judged by Investigator's Global Assessment of response. Luxíq also significantly reduced scaling, erythema, and plaque thickness, as compared with betamethasone valerate

often more locations and clinical investigators than the earlier trials. At least one such trial is required for FDA approval to market a drug.

The rate of completion of our clinical trials depends upon, among other factors, the rate at which patients enroll in the study. Patient enrollment is a function of many factors, including the size of the patient population, the nature of the protocol, the proximity of patients to clinical sites and the eligibility criteria for the study. Delays in planned patient enrollment may result in increased costs and delays, which could have a material adverse effect on our business. In addition, side effects or adverse events that are reported during clinical trials can delay, impede, or prevent marketing approval.

The Food, Drug and Cosmetic Act includes provisions for accelerating the FDA approval process under certain circumstances. For example, we used the so–called 505(b)(2) application process for OLUX, Luxíq, Extina and Actiza, which permitted us in each case to satisfy the requirements for a full NDA by relying on published studies or the FDA's findings of safety and effectiveness based on studies in a previously–approved NDA sponsored by another applicant, together with the studies generated on our products. While the FDA evaluation used the same standards of approval as an NDA, the number of clinical trials required to support a 505(b)(2) application, and the amount of information in the application itself, may be substantially less than that required to support an NDA application. The 505(b)(2) process will not be available for all of our other product candidates, and as a result the FDA process may be longer for our future product candidates than it has been for our products to date.

After we complete the clinical trials of a new drug product, we must file an NDA with the FDA. We must receive FDA clearance before we can commercialize the product, and the FDA may not grant approval on a timely basis or at all. The FDA can take between one and two years to review an NDA, and can take longer if significant questions arise during the review process. In addition, if there are changes in FDA policy while we are in product development, we may encounter delays or rejections that we did not anticipate when we submitted the new drug application for that product. We may not obtain regulatory approval for any products that we develop, even after committing such time and expenditures to the process. Even if regulatory approval of a product is granted, it may entail limitations on the indicated uses for which the product may be marketed.

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Post–Approval Regulation. The FDA continues to review marketed products even after granting regulatory clearances, and if previously unknown problems are discovered or if we fail to comply with the applicable regulatory requirements, the FDA may restrict the marketing of a product or impose the

California and Australia locations, and lower amounts for each of our contract manufacturers, may not completely mitigate the harm to our business from the interruption of the manufacturing of products. The loss of a manufacturer could still have a negative effect on our sales, margins and market share, as well as our overall business and financial results.

If our supply of finished products is interrupted, our ability to maintain our inventory levels could suffer and future revenues may be delayed.

We try to maintain inventory levels that are no greater than necessary to meet our current projections. Any interruption in the supply of finished products could hinder our ability to timely distribute finished products. If we are unable to obtain adequate product supplies to satisfy our customers' orders, we may lose those orders and our customers may cancel other orders and stock and sell competing products. This in turn could cause a loss of our market share and negatively affect our revenues.

Supply interruptions may occur and our inventory may not always be adequate. Numerous factors could cause interruptions in the supply of our finished products including shortages in raw material required by our manufacturers, changes in our sources for manufacturing, our failure to timely locate and obtain replacement manufacturers as needed and conditions affecting the cost and availability of raw materials.

We cannot sell our current products and product candidates if we do not obtain and maintain governmental approvals.

Pharmaceutical companies are subject to heavy regulation by a number of national, state and local agencies. Of particular importance is the FDA in the United States. The FDA has jurisdiction over all of our business and administers requirements covering testing, manufacture, safety, effectiveness, labeling, storage, record keeping, approval, advertising and promotion of our products. If we fail to comply with applicable regulatory requirements, we could be subject to, among other things, fines, suspensions of regulatory approvals of products, product recalls, delays in product distribution, marketing and sale, and civil or criminal sanctions.

The process of obtaining and maintaining regulatory approvals for pharmaceutical products, and obtaining and maintaining regulatory approvals to market these products for new indications, is lengthy, expensive and uncertain. The manufacturing and marketing of drugs, including our products, are subject to continuing FDA and foreign regulatory review, and later discovery of previously unknown problems with a product, manufacturing process or facility may result in restrictions, including withdrawal of the product from the market. The FDA is permitted to revisit and change its prior determinations and it may change its position with regard to the safety or effectiveness of our products. Even if the FDA approves our products, the FDA is authorized to impose post–marketing requirements such as:

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- submitting products for inspection and, if any inspection reveals that the product is not in compliance, prohibiting the sale of all products from the same lot,
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- withdrawing marketing approval.

Even before any formal regulatory action, we could voluntarily decide to cease distribution and sale or recall any of our products if concerns about safety or effectiveness develop.

To market our products in countries outside of the United States, we and our partners must obtain approvals from foreign regulatory bodies. The foreign regulatory approval process includes all of the risks associated with obtaining FDA approval, and approval by the FDA does not ensure approval by the regulatory authorities of any other country.

In its regulation of advertising, the FDA from time to time issues correspondence to pharmaceutical companies alleging that some advertising or promotional practices are false, misleading or deceptive. The FDA has the power to impose a wide array of sanctions on companies for such advertising practices, and if we were to receive correspondence from the FDA alleging these practices we might be required to:

- incur substantial expenses, including fines, penalties, legal fees and costs to comply with the FDA's requirements,
- change our methods of marketing and selling products,
- take FDA–mandated corrective action, which could include placing advertisements or sending letters to physicians rescinding previous advertisements or promotion, and
- disrupt the distribution of products and stop sales until we are in compliance with the FDA's position.

We may spend a significant amount of money to obtain FDA and other regulatory approvals, which may never be granted. Failure to obtain such regulatory approvals could adversely affect our prospects for future revenue growth.

Successful product development in our industry is highly uncertain, and the process of obtaining FDA and other regulatory approvals is lengthy and expensive. Very few research and development projects produce a commercial product. Product candidates that appear promising in the early phases of development may fail to reach the market for a number of reasons, including that the product candidate did not demonstrate acceptable clinical trial results even though it demonstrated positive preclinical trial results, or that the product candidate was not effective in treating a specified condition or illness.

To obtain approval, we must show in preclinical and clinical trials that our products are safe and effective. The FDA approval processes require substantial time and effort, the FDA continues to modify product development guidelines, and we may not be able to obtain FDA approval to conduct clinical trials or to manufacture and market any of the products we develop, acquire or license. Clinical trial data can be the subject of differing interpretation, and the FDA has substantial discretion in the approval process. The FDA may not interpret our clinical data the way we do. The FDA may also require additional clinical data to support approval. The FDA can take between one and two years to review new drug applications, or longer if significant questions arise during the review process. Moreover, the costs to obtain approvals could be considerable and the failure to obtain or delays in obtaining an approval could have a significant negative effect on our business.

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SUBSEQUENT EVENTS

On January 5, 2004, we reached an agreement with S.C. Johnson to terminate an existing license agreement pursuant to which we licensed to S.C. Johnson the rights to a concentrated aerosol spray that is marketed in the U.S. and internationally. On a consolidated basis, in 2003, we received $7.0 million in royalties in connection with this agreement, which included a one–time royalty payment of $2.9 million. In connection with the termination of the agreement, we will cease recognizing royalties after the first quarter of 2004, and S.C. Johnson will have a fully–paid up license to the technology.

On February 9, 2004, we announced that we had entered into a binding purchase agreement with Roche to acquire exclusive U.S. rights to Soriatane–brand acitretin, an approved oral medicine for the treatment of severe psoriasis in adults. The transaction closed on March 4, 2004. Under the terms of the purchase agreement, we paid Roche a total of $123 million in cash at the closing to acquire Soriatane. We also agreed to assume certain liabilities in connection with returns, rebates and chargebacks, and we are obligated to buy Roche's existing inventory within thirty days after the closing of the acquisition.

On February 6, 2004, in connection with the Soriatane acquisition, we entered into a $30 million credit facility provided by Goldman, Sachs Credit Partners L.P. We formally terminated the credit facility on February 25, 2004, without incurring any indebtedness under the facility.

On February 13, 2004, we completed a private placement of 3.0 million shares of our common stock to accredited institutional investors at a price of $20.25 per share, for net proceeds of approximately $57.1 million without giving effect to certain offering costs. We used a portion of the net proceeds to pay for the acquisition of exclusive U.S. rights to Soriatane, and we intend to use the balance for general corporate purposes, including working capital.

CRITICAL ACCOUNTING POLICIES AND ESTIMATES

The fundamental objective of financial reporting is to provide useful information that allows a reader to comprehend our business activities. To aid in that understanding, we have identified our "critical accounting policies and estimates" which are used in preparing the consolidated financial statements. These policies have the potential to have a more significant impact on our financial statements, either because of the significance of the financial statement item to which they relate, or because they require us to make estimates and judgments due to the uncertainty involved in measuring, at a specific point in time, events that are continuous in nature.

Revenue Recognition – Reserves for Discounts, Returns, Rebates and Chargebacks.

We recognize product revenue net of allowances for estimated discounts, returns, rebates and chargebacks. We allow a discount for prompt payment, and we estimate other allowances based primarily on our past experience. We also consider the volume and price mix of products in the retail channel, trends in distributor inventory, economic trends that might impact patient demand for our products (including competitive environment), current arrangements with managed care organizations, the economic value of the rebates being offered and other factors. In the past, actual discounts, returns, rebates and chargebacks have not generally exceeded our reserves. However, actual returns, rebates and chargebacks in the future period are inherently uncertain. Our revenue reserves are approximately 14% of our gross product revenues. If actual returns, rebates and chargebacks are significantly greater than the reserves we have established, the actual results would decrease our reported revenue; conversely, if actual returns, rebates and chargebacks are significantly less than our reserves, this would increase our reported revenue. If we changed our assumptions and estimates, our revenue reserves would change, which would impact the net revenue we report.

We are obligated to accept from customers the return of pharmaceuticals that have reached their expiration date. As a practice, we avoid shipping product that has less than ten months dating. We monitor inventories in the distributor channel to help us assess the rate of return.

We establish and maintain reserves for amounts payable by us to managed care organizations and state Medicaid programs. Generally, we pay managed care organizations and state Medicaid programs a rebate on the prescriptions filled that are covered by the respective programs. We determine the reserve amount at the time of sale based on our best estimate of the expected prescription fill rate to managed care and state Medicaid patients, adjusted to reflect historical experience and known changes in the factors that impact such reserves.

Revenue Recognition – Contract Revenue

We record contract revenue for research and development as it is earned based on the performance requirements of the contract. We recognize royalty revenue in the quarter in which the royalty payment is either received from the licensee or may be reasonably estimated, which is typically one quarter following the related sale by the licensee. We recognize non–refundable contract fees for which no further performance obligations exist, and for which we have no continuing involvement, on the earlier of when the payments are received or when collection is assured. We recognize revenue from non–refundable upfront license fees ratably over the period in which we have continuing development obligations when, at the time the agreement is executed, there remains significant risk due to the incomplete state of the product's development. Revenue associated with substantial "at risk" performance milestones, as defined in the respective agreements, is recognized based upon the achievement of the milestones. We recognize revenue under R&D cost reimbursement contracts as the related costs are incurred.

Goodwill, Purchased Intangibles and Other Long–Lived Assets – Impairment Assessments

We make judgments about the recoverability of goodwill, purchased intangible assets and other long–lived assets whenever events or changes in circumstances indicate an other–than–temporary impairment in the remaining value of the assets recorded on our balance sheet. To judge the fair value of long–lived assets, we make various assumptions about the value of the business that the asset relates to and typically estimate future cash flows to be generated by the asset or, in the case of goodwill, the enterprise. This may include assumptions about future prospects for the asset and typically involves computation of the estimated future cash flows to be generated. Based on these judgments and assumptions, we determine whether we need to take an impairment charge to reduce the value of the asset stated on our balance sheet to reflect its actual fair value. Judgments and assumptions about future values and remaining useful lives are complex and often subjective. They can be affected by a variety of factors, including external factors such as changes in our business strategy and our internal forecasts. Although we believe the judgments and assumptions we have made in the past have been reasonable and appropriate, different judgments and assumptions could materially impact our reported financial results. More conservative assumptions of the anticipated future benefits from these assets would result in greater impairment charges, which would decrease net income and result in lower asset values on our balance sheet. Conversely, less conservative assumptions would result in smaller impairment charges and higher asset values. For more details about how we make these judgments, see *Note 2* in our *Notes to Consolidated Financial Statements.*

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SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this Report to be signed on its behalf by the undersigned, thereunto duly authorized.

Connetics Corporation
a Delaware corporation

By: /s/ John L. Higgins

John L. Higgins
Chief Financial Officer
Executive Vice President, Finance and Corporate Development

Date: March 11, 2004

Each person whose signature appears below constitutes and appoints Katrina J. Church and John L. Higgins, jointly and severally, his or her attorneys–in–fact and agents, each with the power of substitution, for him or her and in his or her name, place or stead, in any and all capacities, to sign any and all amendments to this Annual Report on Form 10–K, and to file the same, with exhibits and other documents in connection therewith, with the Securities and Exchange Commission, granting to each attorney–in–fact and agent, full power and authority to do and perform each and every act and thing requisite and necessary to be done in and about the premises, as fully as he or she might or could do in person, and ratifying and confirming all that the attorneys–in–fact and agents, or his or her substitute or substitutes, may do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this Report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
Principal Executive Officer:		
/s/ Thomas G. Wiggans Thomas G. Wiggans	President, Chief Executive Officer and Director	March 11, 2004
Principal Financial and Accounting Officer:		
/s/ John L. Higgins John L. Higgins	Chief Financial Officer; Executive Vice President, Finance and Corporate Development	March 11, 2004

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Directors:	Signature	Title	Date
/s/ Alexander E. Barkas	Alexander E. Barkas	Director	March 11, 2004
/s/ Eugene A. Bauer	Eugene A. Bauer	Director	March 11, 2004
/s/ R. Andrew Eckert	R. Andrew Eckert	Director	March 11, 2004
/s/ Denise M. Gilbert	Denise M. Gilbert	Director	March 11, 2004
/s/ John C. Kane	John C. Kane	Director	March 11, 2004
/s/ Thomas D. Kiley	Thomas D. Kiley	Director	March 11, 2004
/s/ Leon E. Panetta	Leon E. Panetta	Director	March 11, 2004
/s/ G. Kirk Raab	G. Kirk Raab	Chairman of the Board	March 11, 2004